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# Chronic Anemia in the Newborn Lamb: Cardiovascular Adaptations and Comparison to Chronic Hypoxemia

DANIEL BERNSTEIN, DAVID F. TEITEL, AND ABRAHAM M. RUDOLPH

*Cardiovascular Research Institute and the Departments of Pediatrics, Physiology, and Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, California 94143*

**ABSTRACT. The cardiovascular adaptations to chronic anemia were studied in the newborn lamb and then compared with the adaptations to chronic hypoxemia. Eight chronically instrumented newborn lambs underwent repeat isovolemic exchange transfusions to maintain their Hb concentrations at 60% of normal for age. Hemodynamic studies were performed twice weekly for 2 wk after which time regional blood flows were measured using radionuclide-labeled microspheres. The major compensatory responses after 2 wk of anemia were moderate increases in heart rate (229 ± 20 *versus* 187 ± 15 beats/min) and cardiac output (226 ± 36 *versus* 165 ± 38 ml/kg/min), an increase in fractional extraction of oxygen (65 *versus* 40%), and a redistribution of regional blood flow. Blood flows to the heart and brain increased whereas blood flows to the viscera and carcass did not change. These compensatory responses were different from those that occur during chronic hypoxemia: specifically, cardiac output did increase, growth was not suppressed, and the pattern of redistribution of regional blood flows was different. The dissimilar effects of anemia (decreasing systemic oxygen content ) *versus* hypoxemia (decreasing systemic oxygen tension) on local tissue receptors and peripheral chemoreceptors may account for these differences. (*Pediatr Res* 23: 621–627, 1988)**

During the period of rapid growth after birth, cardiac output and Hb concentration gradually decrease (1). In the presence of a high resting demand for oxygen and a limited ability to further increase cardiac output, this fall in Hb greatly compromises the infant's ability to respond to decreases in systemic oxygen delivery (1–3). When systemic oxygen delivery falls below a critical level, oxygen consumption cannot be maintained and alterations in hemodynamics, metabolism, and growth occur (4, 5).

Whereas previous investigators have studied the effects of acute decreases in systemic oxygen delivery in the newborn (5–7), there are currently few data on the effects of prolonged decreases in systemic oxygen delivery. We have previously studied chronic hypoxemia in the newborn lamb using a model of pulmonary stenosis with atrial right to left shunting (4). In this model the decrease in systemic oxygen tension caused a concomitant decrease in systemic oxygen content. The major compensatory responses were a decrease in growth, an increase in Hb concentration, and a redistribution of regional blood flow (4, 8).

The purpose herein was to determine the relative contributions of reductions in systemic oxygen tension and systemic oxygen content to the compensatory hemodynamic responses and the growth suppression we had observed during chronic hypoxemia. To do this, we created a model of chronic anemia. Using this model we reduced systemic oxygen content comparably to that achieved in the chronic hypoxemia studies (4, 8), but did not decrease systemic arterial oxygen tension. We then compared the compensatory responses to chronic anemia with those to chronic hypoxemia.

## MATERIALS AND METHODS

*Surgical procedure.* Surgery was performed on eight newborn lambs of mixed Western breed within the first 3 days after birth. Under local anesthesia with 0.5% lidocaine hydrochloride, polyvinyl catheters were inserted into a hind leg artery and vein and advanced to the descending aorta and inferior vena cava. The lambs were intubated and ventilated with a Harvard volume-cycled pump respirator (Harvard-Ealing Co., Millis, MA). Under general anesthesia with 1% halothane a thoracotomy was performed in the fourth left intercostal space. Polyvinyl catheters were inserted into the ascending aorta and superior vena cava via the internal thoracic artery and vein and directly into the main pulmonary artery and left atrium. A precalibrated electromagnetic flow transducer (C & C Instruments, Culver City, CA) was placed around the ascending aorta. A no. 8 French polyvinyl catheter chest tube was inserted into the left pleural cavity and the chest was closed in layers. All catheters were filled with heparin and plugged, brought to the skin via a subcutaneous tunnel, and protected by a bag sewn to the lamb's flank. The lambs were returned to their ewes and remained with them throughout the 2-wk study period. The intravascular catheters were flushed with saline and reheparinized daily for the first 5 days and twice weekly thereafter. The lambs received intramuscular antibiotics (1 ml of Combiotic, Henry Schein Inc., Port Washington, NY) immediately preceding catheter flushing. Intramuscular iron dextran complex (equivalent to 100 mg of elemental iron) was given weekly to avoid the hemodynamic effects of iron deficiency (9, 10).

*Production of anemia.* After 3 days of recovery, an isovolemic exchange transfusion was performed using fresh lamb plasma, supplemented with Dextran 40 (Gentran, Travenol, Deerfield, IL) as needed. The volume of the exchange was calculated to drop the Hb concentration, and thus the oxygen carrying capacity, to 60% of normal. This was calculated based on the normal values reported by Lister *et al.* (1), to be a Hb concentration of approximately 6 g/dl during the 1st wk of life and 5 g/dl during the 2nd and 3rd wk of life. The lamb's whole blood that was

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Correspondence and reprints Daniel Bernstein, M.D., Department of Pediatrics—S348, Stanford University Medical Center, Stanford, CA 94305.
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removed during the exchange transfusion was then centrifuged and the plasma saved for subsequent transfusions. Repeat isovolemic exchange transfusions were performed every 2 days, as needed, to maintain this degree of anemia for a period of 2 wk.

*Experimental protocol.* Before the onset of anemia, and then twice weekly, each lamb was weighted, blindfolded, and placed in a sling under a radiant warmer that maintained environmental temperature between 24 and 27° C (11). All vascular catheters were connected to Statham P23Db pressure transducers (Statham Instruments, Oxnard, CA). After the lamb was resting quietly, aortic, pulmonary arterial, left atrial, and central venous pressures were recorded on a Beckman 8 channel direct writing recorder (Beckman Instruments, San Jose, CA). Ascending aortic blood flow was recorded with the electromagnetic flow transducer connected to a Statham SP2202 flowmeter (Statham Instruments). Oxygen consumption was measured by placing a loose-fitting bag around the lamb's head and analyzing expired gas according to the method of Lister *et al.* (12). Aortic and pulmonary arterial blood samples were withdrawn simultaneously for measurement of blood gases (Corning 158 pH/blood gas analyzer, Medfield, MA), Hb concentration and oxygen saturation (Radiometer OSM 2 hemoximeter, Copenhagen, Denmark), hematocrit, and estimation of total serum protein (American Optical Corporation Refractometer, Buffalo, NY).

After 2 wk of anemia, regional blood flows were measured. To avoid changes in gastrointestinal tract blood flow associated with recent oral intake (13), the lambs were studied at least 2 h after being separated from their mothers. Fifteen $\mu$m diameter radionuclide-labeled microspheres (labeled with one of the following radionuclides: $^{153}$Gd, $^{57}$Co, $^{114}$In, $^{51}$Cr, $^{113}$Sn, $^{85}$Sr, $^{95}$Nb, $^{54}$Mn, or $^{65}$Zn) were injected into the left atrium while reference blood samples were withdrawn continuously and simultaneously from the ascending and descending aortic catheters into preweighed syringes for 1.5 min at a rate of 4 ml/min (14). This rate of withdrawal is adequate to avoid artifacts related to the nonhomogeneous distribution of microspheres during anemia (15). At the end of the study the lamb was killed and dissected. The skin was separated from the remainder of the carcass. Each organ and organ part, the carcass, and the skin were weighed and incinerated. The radioactivity of each part was then counted on a gamma counter with a multichannel pulse height analyzer (14). To demonstrate a correlation between the two methods of measuring cardiac output in this model, we measured ascending aortic blood flow with the electromagnetic flowmeter (which excludes coronary blood flow) and cardiac output with microspheres simultaneously at the end of the 2 wk of anemia. If coronary blood flow (averaging 8.5% of cardiac output in the anemic lambs) was added to the flow probe blood flow, there was a mean absolute difference of 14 ± 8% between the two measurements, with only one difference greater than 20% and none greater than 30%. This degree of correlation is consistent with the findings of Kuipers *et al.* (16).

*Calculations.* Aortic and pulmonary arterial oxygen content were calculated as the product of the Hb concentration, Hb oxygen saturation, and a Hb oxygen binding capacity of 1.36 ml oxygen/dl. Systemic oxygen delivery was calculated as the product of systemic blood flow and aortic oxygen content. Extraction coefficient was calculated as the arteriovenous oxygen difference divided by aortic oxygen content. P50 was calculated from the oxygen saturations and tensions of three simultaneous blood samples using regression analysis.

Organ blood flow was calculated as the product of recovered radioactivity counts from each organ or organ part and reference sample blood flow divided by reference sample counts. Percent of total cardiac output to each organ or vascular bed was calculated by dividing individual organ counts by total recovered counts. Oxygen delivery to each organ was calculated as the product of the microsphere-derived blood flow to that organ and aortic oxygen content. Systemic vascular resistance was calculated as the difference between aortic mean pressure and central venous pressure divided by cardiac output. Because of the wide variability in the sizes of the lambs, organ weights were normalized by calculating organ weight as a percentage of total body weight.

*Analysis.* The data from the anemic lambs were compared to the previously reported data from 11 chronically hypoxemic lambs (4, 8). Chronic hypoxemia was produced by surgical creation of supravalvar pulmonic stenosis and an atrial septal defect (4). Aortic oxygen saturation was decreased to between 60 and 74% and was maintained at this level for 2 wk. Data from the anemic lambs were also compared to previously reported data from 12 control lambs, which had undergone similar surgery (4, 8).

Data from the anemic lambs were divided into subgroups according to the duration of anemia on the day the data were obtained. This method of analysis was performed to compare results chronologically with the hypoxemic lambs (4, 8). The data were divided into six subgroups. The first subgroup of measurements was performed immediately before the first exchange transfusion, the second after 1 to 3 days of anemia, the third after 4 to 6 days of anemia, the fourth after 7 to 9 days, the fifth after 10 to 12 days, and the sixth after 13 or more days of anemia. The data were analyzed in two ways. First, when comparing the anemic, hypoxemic, and control lambs, statistical analysis was performed using analysis of variance with Student-Newman-Keuls multiple range testing. The data are plotted by age with the subgroups representing the duration of anemia shown by a point at the mean age for each subgroup. In Figure 1, the average duration of anemia is shown above each subgroup. Second, when comparing only the anemic and hypoxemic lambs, statistical analysis was performed by Student's nonpaired $t$ test and the data are plotted by days anemic or hypoxemic. Statistical significance was considered achieved when $p$ was $<0.05$. All values in the text are reported as means with 1 SD.

## RESULTS

*General.* All eight anemic lambs survived the initial exchange transfusion. Two lambs died during the study period. These lambs were not different from the survivors with respect to degree of anemia, arterial and mixed venous blood gases, aortic blood flow, oxygen consumption, or growth. In comparison, none of the control lambs died. The ages at which regional blood flows were measured were similar (anemic 27 ± 5.8 days, control 26.7 ± 5.5 days, nonsignificant by Student's $t$ test).

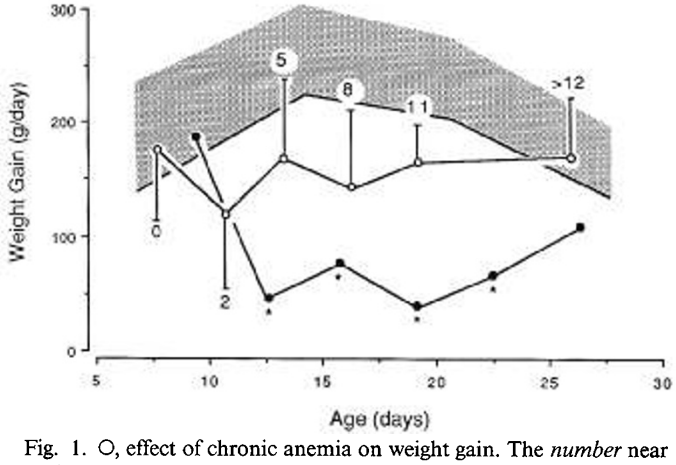


Fig. 1. ○, effect of chronic anemia on weight gain. The *number* near each *data point* represents the mean duration of anemia in that subgroup. ●, data from chronically hypoxemic lambs are reproduced from Teitel *et al.* (4). SD are not shown for hypoxemic lambs to improve clarity. Also shown is the mean (*solid line*) and 1 SD above the mean for the control group (*shaded area*). *$p < 0.05$ by analysis of variance.

Weight gain in the anemic lambs was similar to the controls throughout the study period, with the exception of a brief decrease immediately after the onset of anemia (Fig. 1). (In all figures, data from the anemic lambs are compared with previously published data from the hypoxemic lambs (4, 8). Comparisons between these two experiments are presented in the "Discussion.") Heart rate was initially higher in the anemic lambs, which failed to show the normal decrease in heart rate with age seen in the controls (Table 1). Aortic systolic, diastolic, and mean pressures, and total systemic vascular resistance were not significantly different from control (Table 1). Oxygen half-saturation pressure of Hb increased, similar to the increase seen in normal lambs (1, 6). Total serum protein decreased slightly throughout the study in the anemic lambs.

*Oxygen delivery.* Hb concentration was maintained at a consistently low level in the anemic lambs (Fig. 2*A*) whereas systemic arterial oxygen saturation was normal (Fig. 2*B*). Thus, systemic arterial oxygen content was reduced for the duration of the study (Fig. 2*C*). Cardiac output decreased initially in the anemic lambs and then increased to above control level (Fig. 3*A*). Cardiac output in the control lambs showed the normal decrease associated with increasing age. Despite the decrease in systemic oxygen content, by the end of 2 wk systemic oxygen transport was not different from control, due to the increase in cardiac output (Fig. 3*B*).

*Oxygen utilization.* Total body oxygen consumption indexed to weight dropped gradually over the study period and was similar to that found by Lister *et al.* (1) in normal lambs (Fig. 4*A*). Fractional extraction of oxygen was elevated to approximately 65% in the anemic lambs *versus* 35–43% seen normally (1) (Fig. 4*B*). Mixed venous oxygen tension [an index of tissue oxygenation (17)], mixed venous oxygen saturation, and mixed venous oxygen content were all decreased (Fig. 5).

*Regional blood flows and oxygen delivery.* Blood flows to the heart and brain were increased in the anemic lambs (Fig. 6). Blood flows to the gastrointestinal tract, liver, and carcass were not different from control (Fig. 6). Adrenal, splenic, and renal blood flows were also not statistically different from control (not shown). Oxygen delivery was maintained to the heart, brain, and adrenals and was decreased to the spleen, kidneys, gastrointestinal tract, and carcass (Fig. 7). There were no significant differences between anemic and control lambs in individual organ weights expressed as a percentage of total body weight except for skin weight which was slightly greater in the anemic lambs (Fig. 8).

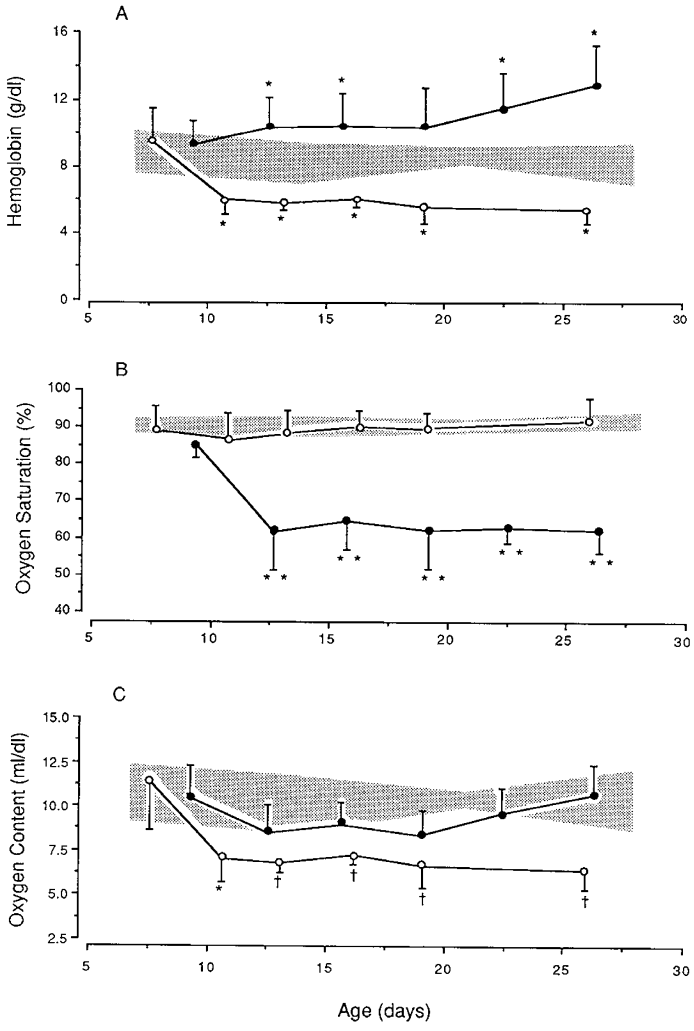


Fig. 2. O, effect of chronic anemia on (*A*) Hb concentration; (*B*), arterial oxygen saturation; and (*C*), arterial oxygen content. Data are compared to chronic hypoxemia (●) (4) and to control (*shaded area* represents 1 SD above and below the mean). *$p < 0.05$ *versus* control; **$p < 0.05$ *versus* control and anemic; †$p < 0.05$ *versus* control and hypoxemic by analysis of variance.

Table 1. *Hemodynamic characteristics of anemic lambs compared with hypoxemic lambs and controls (mean and 1 SD)*

| | Baseline | | | 1 Wk | | | 2 Wk | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Anemic | Hypoxemic | Control | Anemic | Hypoxemic | Control | Anemic | Hypoxemic |
| Heart rate (bpm) | 232 | 261† | 228 | 212 | 241 | 249* | 187 | 229* | 238* |
| | (29) | (20) | (27) | (23) | (18) | (35) | (15) | (20) | (18) |
| Aortic pressure (mm Hg) | | | | | | | | | |
| Systolic | 100 | 97 | 96 | 104 | 114 | 97 | 102 | 93 | 109 |
| | (9) | (15) | (10) | (12) | (26) | (18) | (16) | (17) | (23) |
| Diastolic | 70 | 67 | 66 | 69 | 77 | 69 | 72 | 66 | 77 |
| | (6.3) | (7) | (8) | (9) | (18) | (15) | (12) | (12) | (15) |
| Mean | 75 | 80 | 77 | 82 | 81 | 79 | 74 | 77 | 88 |
| | (9) | (11) | (7) | (14) | (24) | (16) | (10) | (11) | (15) |
| Systemic vascular resistance (mm Hg/ml/min/kg) | 0.24 | 0.29 | 0.27 | 0.32 | 0.44 | 0.31 | 0.40 | 0.35 | 0.40 |
| | (0.05) | (0.09) | (0.12) | (0.12) | (0.25) | (0.15) | (0.10) | (0.11) | (0.20) |
| Oxygen half-saturation pressure of Hb | | 34.2 | 36.8 | | 40.9 | 38.8 | | 40.8 | 39.8 |
| | | (2.8) | (4.0) | | (4.6) | (3.7) | | (3.8) | (1.0) |
| Total serum protein concentration (g/dl) | | 5.7 | 6.1 | | 5.4 | 5.9 | 5.9 | 5.1† | 6.4 |
| | | (0.8) | (0.5) | | (0.5) | (0.3) | (0.6) | (0.4) | (0.2) |

* $p < 0.05$ *versus* control; † $p < 0.05$ *versus* hypoxemic and control.

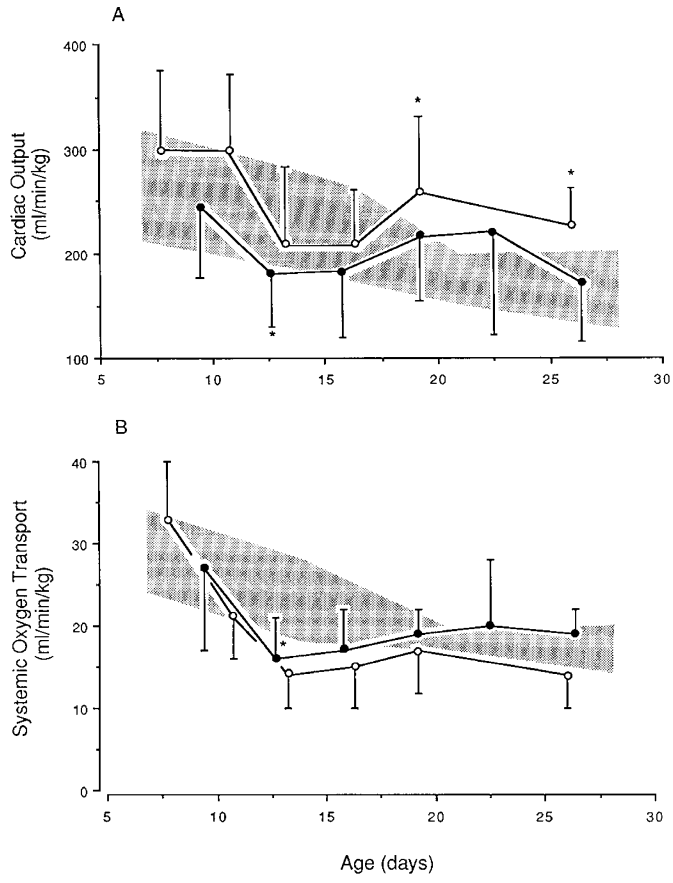


Fig. 3. O, effect of chronic anemia on (*A*) cardiac output and (*B*) systemic oxygen transport; compared with chronic hypoxemia (●) (4) and controls (*shaded area*). *$p < 0.05$ *versus* control by analysis of variance.

## DISCUSSION

The major compensatory responses to chronic anemia in the newborn lamb were increases in heart rate, cardiac output, and fractional extraction of oxygen. Because of the increase in cardiac output, total body oxygen delivery was normal. There were, however, important regional alterations in oxygen delivery caused by the redistribution of regional blood flow. Blood flows to the heart and brain increased, so that oxygen delivery to these organs was maintained at a normal level; however, because blood flows to the carcass and visceral organs did not increase, oxygen delivery to these organs was less than normal. Despite this decrease in peripheral and visceral oxygen delivery, growth was not suppressed.

There are important similarities and differences between the compensations to chronic anemia in the newborn lamb and those described in previous studies in adult dogs (18) and in adult humans (19). The moderate increases in cardiac output and fractional extraction of oxygen are similar to those described in adult humans by Woodson *et al.* (19), except that in these adults the increase in cardiac output was due to an increase in stroke volume rather than heart rate (19). This difference from the results herein may be due to developmental differences in the mechanisms by which cardiac output can be most effectively increased in the newborn *versus* the adult (3, 20).

Redistribution of regional blood flow during chronic anemia has been previously described in adult dogs (18), but the pattern of this redistribution is somewhat different from that which we found in newborn lambs. Myocardial blood flow increased and mesenteric blood flow did not change, as in the lamb, but unlike in the lamb, renal blood flow decreased and hindlimb blood flow increased (18). This difference in the peripheral blood flow response may be due to developmental differences in peripheral autonomic or local tissue responses to chronic anemia, to differences in the degree of anemia (less severe in our study), or to the possibility that hindlimb blood flow may not be representative of blood flow to the carcass as a whole.

We also compared the major compensatory responses during chronic anemia with those that we had previously reported during chronic hypoxemia (4). In contrast to the normal growth seen during chronic anemia, chronic hypoxemia is associated with marked growth suppression (Fig. 1). One of the major compensatory responses to chronic hypoxemia is an increase in Hb concentration (Fig. 2*A*). Because of this increase in blood oxygen-carrying capacity in the hypoxemic group, by the end of the 2 wk of study, systemic oxygen content returned to normal in the hypoxemic lambs while remaining low in the anemic

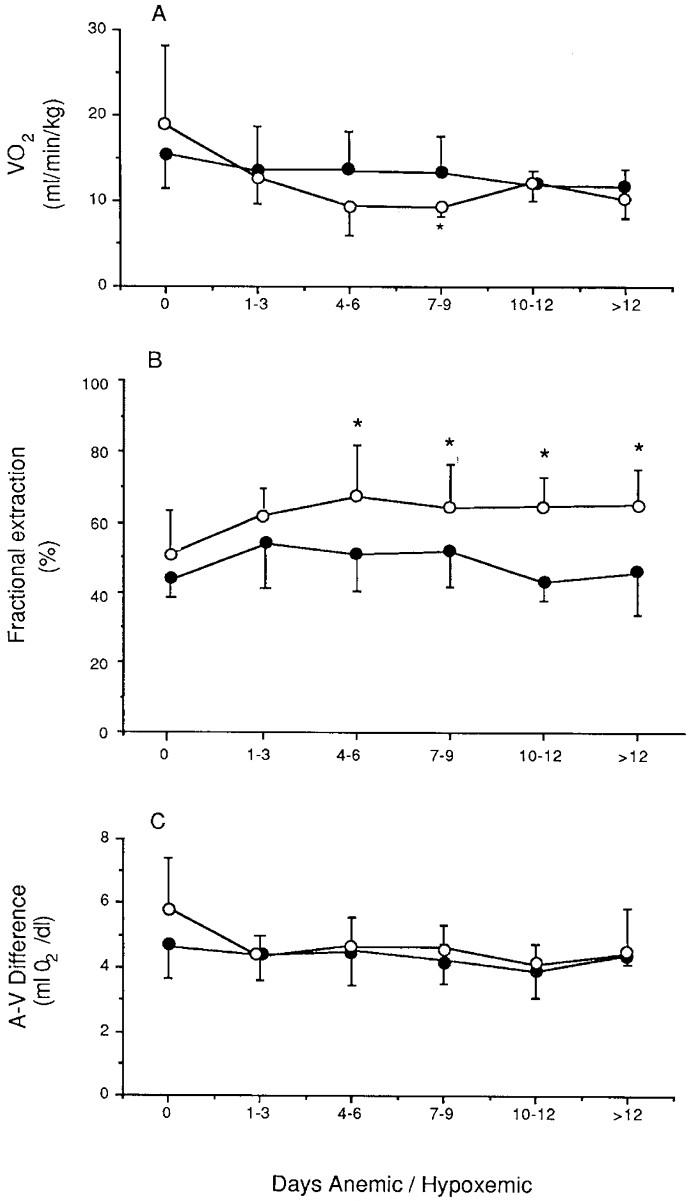


Fig. 4. O, effect of chronic anemia on oxygen utilization plotted by days anemic (*abscissa*) and compared to chronic hypoxemia (●) (4). *$p < 0.05$ *versus* hypoxemic by nonpaired *t* test.

lambs (Fig. 2*C*). Heart rate is elevated during chronic hypoxemia, similar to chronic anemia (Table 1); however, because of a decrease in stroke volume during chronic hypoxemia, cardiac output was not increased above normal (Fig. 3*A*). Thus, systemic oxygen transport returns to control levels in both chronic anemia and chronic hypoxemia, but by different compensatory mechanisms: cardiac output increased in the anemic lambs whereas Hb concentration increased in the hypoxemic lambs (Fig. 3*B*).

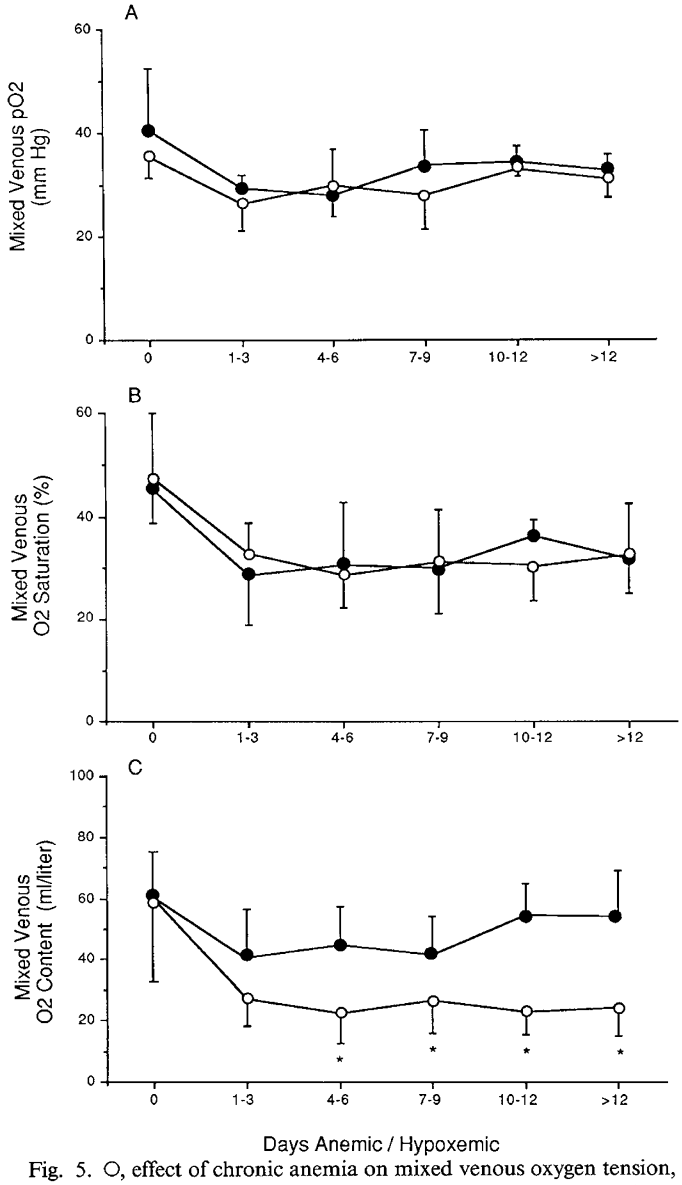


Fig. 5. ○, effect of chronic anemia on mixed venous oxygen tension, saturation, and content compared to chronic hypoxemia (●) (4). *$p <$ 0.05 *versus* hypoxemic by nonpaired *t* test.

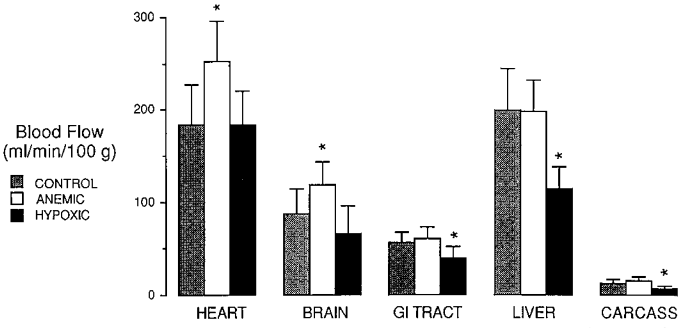


Fig. 6. Redistribution of regional blood flow during chronic anemia compared with chronic hypoxemia (hypoxemic data from Bernstein *et al.* (8) and controls. *$p < 0.05$ by analysis of variance.

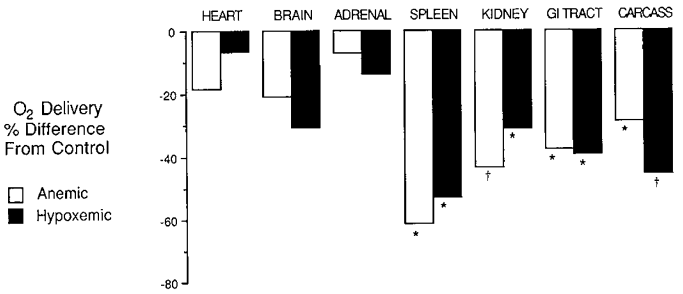


Fig. 7. Percent change in regional oxygen delivery during chronic anemia compared with chronic hypoxemia (8). *$p < 0.05$, †$p < 0.005$ *versus* control by analysis of variance.

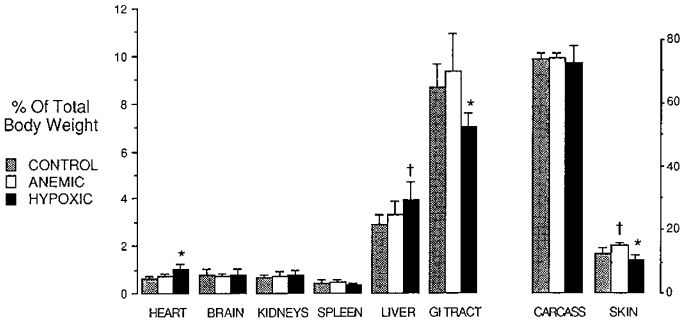


Fig. 8. Organ weights as a percentage of total body weight during chronic anemia compared with chronic hypoxemia and controls [data from Bernstein *et al.* (8)]. Note the change in scale on the right of the figure for carcass and skin weights. *$p < 0.05$ *versus* control and anemia; †$p < 0.05$ *versus* control by analysis of variance.

Total body oxygen consumption indexed to weight was not different between the anemic and hypoxemic lambs (Fig. 4*A*). Fractional extraction of oxygen is increased during chronic hypoxemia, although significantly less than in chronic anemia (Fig. 4*B*). Inasmuch as fractional extraction of oxygen is equal to oxygen consumption divided by systemic oxygen transport, this difference may have been due to the slightly lower systemic oxygen transport in the anemic lambs, which was independently not significantly different from the values of the hypoxemic lambs. The actual amount of oxygen extracted, or arteriovenous oxygen difference, was not different between the two groups (Fig. 4*C*). Mixed venous oxygen tension and saturation were equally reduced in both anemic and hypoxemic lambs (Fig. 5 *A* and *B*); however, because of the much higher Hb concentration in the hypoxemic lambs, mixed venous oxygen content returned to normal in this group (Fig. 5*C*).

Regional blood flow distribution is also markedly different in chronic anemia from that seen during chronic hypoxemia (8). During chronic hypoxemia, blood flow to the heart and brain is not increased, and blood flow to the gastrointestinal tract, liver, and carcass is decreased (Fig. 6). This difference in the redistribution of blood flow between chronic anemia and chronic hypoxemia may be related to the mechanisms by which blood flow to different organs is regulated. The heart and brain compensate for a decrease in oxygen delivery primarily by increasing blood flow in response to tissue hypoxemia (2, 21–24); peripheral chemoreceptor stimulation does not play a major role in this response (25–27). During both acute anemia and acute hypoxemia systemic arterial oxygen content is decreased, so that myocardial and cerebral blood flows must increase to maintain local

oxygen delivery. During chronic anemia, systemic arterial oxygen content remains decreased, so that the increases in myocardial and cerebral blood flows persist. During chronic hypoxemia, however, the increase in Hb concentration returns systemic arterial oxygen content to normal, so that blood flow to the myocardium and brain need not increase to maintain oxygen delivery (8).

The gastrointestinal tract and carcass respond to a decrease in oxygen delivery through a complex series of responses which serve to increase oxygen extraction (2, 28–30). Blood flow is regulated by changes in local tissue metabolism and by changes in arterial, venous, and tissue pressures (31, 32). However, unlike the heart and brain, peripheral chemoreceptor stimulation also plays a major role in blood flow regulation to the gastrointestinal tract and carcass (27). During chronic anemia, arterial oxygen tension is normal and there is stimulation of sympathetic nervous input to the carotid chemoreceptors, so that there is little or no increase in carotid chemoreceptor activity (33–35) and no peripheral vasoconstriction. During chronic hypoxemia, arterial oxygen tension is decreased, resulting in chemoreceptor stimulation and vasoconstriction of the cutaneous and possibly also the visceral circulations (8). Despite this difference in blood flow, oxygen delivery to the viscera and carcass is decreased similarly in chronic anemia and chronic hypoxemia, because of the decreased systemic oxygen content during chronic anemia and the decreased blood flow in chronic hypoxemia.

We did not see suppression of growth during chronic anemia despite the fact that suppression of growth did occur during chronic hypoxemia at a similar reduction of systemic oxygen transport. We can speculate on several possible explanations for this difference in growth. First, although we did not quantify either ventilation or caloric intake, the hypoxemic lambs were subjectively more tachypneic than the anemic lambs (4). Thus, the portion of total body oxygen consumption devoted to cardiorespiratory work may have been higher in the hypoxemic than in the anemic lambs. Additionally, the increased work of breathing may have made feeding more difficult in the hypoxemic group. Inadequate caloric intake has been shown to contribute to growth failure in chronic alveolar hypoxemia (36). Second, the decrease in blood flow, and possibly also in substrate delivery, to the gastrointestinal tract and carcass seen exclusively in the hypoxemic lambs may have been responsible for their decreased rate of growth. Reduced blood flow to the gastrointestinal tract has been shown to impair motility (29) and reduced peripheral blood flow has been previously suggested, but not documented, as a potential cause of growth failure in congenital heart disease (37). It is intriguing in this regard that in the hypoxemic lambs the gastrointestinal tract and skin weights were a disproportionately smaller percentage of total body weight than in the anemic or control lambs (Fig. 8). Finally, the metabolic signal responsible for the decrease in growth may be oxygen tension dependent, and thus not affected by anemia. The latter mechanism seems least likely given normal fetal growth in a low oxygen tension environment. However, it is not known whether the hormonal regulators of growth in the newborn, which differ from those in the fetus, are more sensitive to lowered oxygen tension.

In conclusion, the major compensatory responses to chronic anemia in the newborn period are moderate increases in heart rate and cardiac output, an increase in fractional extraction of oxygen, and a redistribution of regional blood flow. Thus, during chronic anemia, as in chronic hypoxemia (8), determinations of total body oxygen consumption or oxygen delivery may not reflect important regional variations related to the redistribution of cardiac output. The compensatory responses during chronic anemia, including the pattern of redistribution of regional blood flow, are different from those occurring during chronic hypoxemia. The dissimilar effects of decreases in systemic oxygen content and systemic oxygen tension on local tissue receptors and peripheral chemoreceptors may account for these differences. Although some of the costs of chronic anemia are comparable to the costs of chronic hypoxemia, there is an additional cost during chronic hypoxemia, the suppression of growth, which does not occur during chronic anemia.

## REFERENCES


1. Lister G, Walter TK, Versmold HT, Dallman PR, Rudolph AM 1979 Oxygen delivery in lambs: cardiovascular and hematologic development. Am J Physiol 237:H668–H675
2. Rudolph AM 1984 Oxygenation in the fetus and neonate—a perspective. Semin Perinatol 8:158–167
3. Teitel DF, Sidi D, Chin T, Brett C, Heymann MA, Rudolph AM 1985 Developmental changes in myocardial contractile reserve in the lamb. Pediatr Res 19:948–955
4. Teitel DF, Sidi D, Bernstein D, Heymann MA, Rudolph AM 1985 Chronic hypoxemia in the newborn lamb: cardiovascular, hematopoietic, and growth adaptations. Pediatr Res 19:1004–1010
5. Fahey JT, Lister G 1985 A simple method for reducing cardiac output in the conscious lamb. Am J Physiol 249:H188–H192
6. Sidi D, Kuipers JRG, Teitel D, Heymann MA, Rudolph AM 1983 Developmental changes in oxygenation and circulatory responses to hypoxemia in lambs. Am J Physiol 245:H674–H682
7. Weismann DN 1982 Tissue oxygen delivery in lambs: effect of postnatal age and acute hypoxemia. Biol Neonate 42:15–21
8. Bernstein D, Teitel DF, Sidi D, Heymann MA, Rudolph AM 1987 Redistribution of regional blood flow and oxygen delivery in experimental cyanotic heart disease in newborn lambs. Pediatr Res 22:389–393
9. Finch CA, Miller LR, Inamdar AR, Person R, Seiler K, Mackler B 1976 Iron deficiency in the rat: physiological and biochemical studies of muscle dysfunction. J Clin Invest 58:447–453
10. Voorhees ML, Stuart MJ, Stockman JA, Oski FA 1975 Iron deficiency anemia and increased urinary norepinephrine excretion. J Pediatr 86:542–547
11. Sidi D, Kuipers JRG, Heymann MA, Rudolph AM 1983 Effects of ambient temperature on oxygen consumption and the circulation in newborn lambs. Am J Physiol 245:H674–H682
12. Lister G, Hoffman JIE, Rudolph AM 1974 Oxygen uptake in infants and children: a simple method for measurement. Pediatrics 53:656–662
13. Edelstone DI, Holzman IR 1981 Gastrointestinal tract O2 uptake and regional blood flows during digestion in conscious newborn lambs. Am J Physiol 241:G289–G293
14. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM 1977 Blood flow measurement with radionuclide-labelled particles. Prog Cardiovasc Dis 20:55–79
15. Rosenberg AA, Jones Jr MD, Koehler RC, Traystman RJ, Lister G 1983 Precautions for measuring blood flow during anemia with the microsphere technique. Am J Physiol 244:H308–H311
16. Kuipers JRG, Sidi D, Heymann MA, Rudolph AM 1982 Comparison of methods of measuring cardiac output in newborn lambs. Pediatr Res 16:594–598
17. Tenney SM 1974 A theoretical analysis of the relationship between venous blood and mean tissue oxygen pressures. Respir Physiol 20:283–296
18. Vatner SF, Higgins CB, Franklin D 1972 Regional circulatory adjustments to moderate and severe chronic anemia in conscious dogs at rest and during exercise. Circ Res 30:731–739
19. Woodson RD, Wills RE, Lenfant C 1978 Effect of acute and established anemia on O2 transport at rest, submaximal and maximal work. J Appl Physiol 44:36–43
20. Romero TE, Friedman WF 1979 Limited left ventricular response to volume overload in the neonatal period: a comparative study with the adult animal. Pediatr Res 13:910–915
21. Fisher DJ, Heymann MA, Rudolph AM 1982 Fetal myocardial oxygen and carbohydrate consumption during acutely induced hypoxemia. Am J Physiol 242:H647–H661
22. Feinberg H, Gerola A, Katz LN 1958 Effect of hypoxia on cardiac oxygen consumption and coronary flow. Am J Physiol 195:593–600
23. Jones Jr MD, Sheldon RE, Peeters LL, Meschia, G, Battaglia FC, Makowski EL 1977 Fetal cerebral oxygen consumption at different levels of oxygenation. J Appl Physiol 43:1080–1084
24. Jones Jr MD, Traystman RJ 1984 Cerebral oxygenation of the fetus, newborn, and adult. Semin Perinatol 8:205–216
25. Krasney JA, Koehler RC 1977 Influence of arterial hypoxia on cardiac and coronary dynamics in the conscious sinoaortic-denervated dog. J Appl Physiol 43:1012–1018
26. Traystman RJ, Fitzgerald RS, Loscutoff SC 1978 Cerebral circulatory responses to arterial hypoxia in normal and chemodenervated dogs. Circ Res 42:648–657
27. Heistad DD, Abboud FM 1980 Circulatory adjustments to hypoxia. Circulation 61:463–470
28. Edelstone DI, Lattanzi DR, Paulone ME, Holzman IR 1983 Neonatal intestinal oxygen consumption during arterial hypoxemia. Am J Physiol 244:G278–G283
29. Szabo JS, Stonestreet BS, Oh W 1985 Effects of hypoxemia on gastrointestinal blood flow and gastric emptying in the newborn piglet. Pediatr Res 19:466–

471
30. Holzman IR 1984 Fetal and neonatal hepatic perfusion and oxygenation. Semin Perinatol 8:234–244
31. Johnson PC 1986 Autoregulation of blood flow. Circ Res 59:483–495
32. Duling BR, Hogan RD, Langille BL, Lelkes P, Segal SS, Vatner SF, Weigelt H, Young MA 1987 Vasomotor control: functional hyperemia and beyond. Fed Proc 46:251–263
33. Hatcher JD, Chiu LK, Jennings DB 1978 Anemia as a stimulus to aortic and carotid chemoreceptors in the cat. J Appl Physiol 44:696–702
34. Borison HL, Hurst JH, McCarthy LE 1982 Respiration unaffected by anemia in chemodenervated cats. Respiration 43:1–7
35. Vijaylaxmi N, Pande JN, Gupta SP, Guleria JS 1978 Peripheral chemoreceptor insensitivity in chronic severe anemia. Respiration 35:37–39
36. Elliott DA, Cheek DB 1968 Muscle and liver cell growth in rats with hypoxia and reduced nutrition. In: Cheek DB (ed) Human Growth. Lea & Febiger, Philadelphia, pp 326–336
37. Gingell RL, Pieroni DR, Hornung MG 1981 Growth problems associated with congenital heart disease in infancy. In: Lebanthal E (ed) Textbook of Gastroenterology and Nutrition in Infancy. Raven Press, New York, pp 853–860