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J Clin Invest. 1969;48(10):1862-1869. <https://doi.org/10.1172/JCI106152>.

Research Article

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When systemic O₂ consumption was increased acutely by muscular exercise, cardiac output increased, and the changes in blood L/P were small and not consistent between different dogs. But when O₂ supply to the tissues was simultaneously limited by anemia, L/P increased during exercise, and the magnitude of the increase was proportional to the severity of the anemia. These results suggest that changes in blood L/P during exercise are related specifically to tissue O₂ supply.

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Effect of Decreased O₂ Supply to Tissue on the Lactate:Pyruvate Ratio in Blood

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ABSTRACT Experiments were performed with trained conscious dogs with permanently implanted intravascular catheters. With the dogs in a basal resting state, the concentrations of lactate (L) and pyruvate (P) in arterial blood fluctuated widely from day to day, whereas their concentration ratio (L/P) remained relatively constant. By contrast, decrease in tissue O₂ supply induced by severe chronic anemia increased the arterial blood L/P, specifically, with only random accompanying changes in the lactate or pyruvate concentrations themselves.

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INTRODUCTION

Although O₂ transport via blood can be readily measured in a living body, there is no equally satisfactory method to determine changes in the availability of O₂ for metabolism within the body tissue. Since the ratio between lactate and pyruvate concentrations (L/P) is linked to the oxidation-reduction balance of the respiratory enzyme system, it might be possible to detect decreased O₂ availability for metabolism or tissue hypoxia by an increase in blood L/P. Several investigators have shown that when O₂ supply is decreased acutely by ischemia, hypoxemia, or anemia, the blood L/P promptly increases

Peter E. Jensen, Gerald B. Rich, and John D. Werschkul were Student Fellows supported by the Oregon Heart Association.

Received for publication 28 April 1969.

(1-5). Since the supply of O₂ to the tissue via the blood clearly was decreased in these experiments, here tissue hypoxia stands as a reasonable explanation for the increased blood L/P.

Other authors, however, have emphasized the complicated nature of the relationship between blood L/P and the oxidation-reduction balance of the tissue respiratory enzyme system, and they have questioned whether an increase in blood L/P can, as a rule, be regarded as evidence of tissue hypoxia (6, 7). Moreover, in some conditions where tissue hypoxia might be expected, especially chronic tissue hypoxia, changes reported in blood L/P have been inconsistent (8-13).

Our objective is to determine whether the relationship between tissue hypoxia and increased blood L/P extends beyond the limited experimental conditions in which it already has been demonstrated. Initially, we investigated the effect of factors other than tissue hypoxia by determining the extent of variability in blood L/P when these factors were allowed to vary spontaneously from one day to the next. Subsequently, we determined the changes in blood L/P during two different conditions in which tissue hypoxia could be expected: (a) severe chronic anemia, and (b) restricted O₂ supply via the blood while tissue O₂ consumption was acutely increased by muscular exercise. To secure information under physiologic conditions that should be broadly applicable, we carried out these experiments in trained dogs without anesthesia.

METHODS

Preparation of animals

12 male dogs, each weighing 22-24 kg, were trained to lie still for an hour or more without restraint. Four of them were trained also to run on a treadmill. Subsequently, they were anesthetized with pentobarbital, and silastic catheters (0.04 inch I.D., Dow Corning Corp., Midland, Mich.) were positioned in the pulmonary artery and the thoracic aorta via neck vessels. The proximal ends of the catheters

emerged at the back, where they were secured to the skin. Plastic stub needles with rubber stoppers glued into their large ends were fixed to the proximal ends of the catheters. We sampled blood by puncturing the rubber stopper. The use of this arrangement without disturbing the dog has been described (14).

Experimental protocol

Chronic anemia. In dog Nos. 1-8, initial control observations were repeated on from 6 to 25 days during 2-8 wk. Seven of these dogs were made anemic during a 30 hr period by repeated removal of 300-ml increments of blood through the aortic catheter, with reinfusion of the separated plasma at each step. The hemoglobin concentration was reduced to 7.1 g in dog No. 1 and to levels ranging from 2.7 to 4.8 g/100 ml in dog Nos. 2-7. Subsequently, the hemoglobin was kept at a constant depressed level for 5 wk by bleeding 80-120 ml/day. Observations were made at least twice weekly during the 5 anemia wk. Dog No. 8 was studied for a comparable period without anemia. In dog Nos. 4-7, at the end of 5 wk of anemia, 250 mg of iron (Imferon, Lakeside Laboratories, Inc., Milwaukee, Wis.) and 400-600 ml of matched blood were given, and recovery control observations made.

We studied the dogs while they lay at rest in the post-absorptive state. Immediately after his daily 5 min morning walk, the dog entered a quiet room where he lay, facing the wall, on his side on a low bench. Sampling tubes were connected to his catheter adapters and the dog relaxed for 10-15 min before observations began. The dog was ignored throughout. No restraint, sedative, or reassurance was employed, and the dog seldom moved.

Exercise experiments were performed in dog Nos. 9-12, first on 2-4 days with the dogs not anemic and then at increasingly severe levels of anemia, induced in four steps of 1 day each. After observations were made as above with the dog lying at rest, the dog entered another room and was harnessed to a motor-driven treadmill. A second set of

TABLE I

L/P of Red Cell and Plasma Components of Whole Blood

	Lactate	Pyruvate	L/P
	<i>mmole/liter</i>		
RBC	0.318	0.052	6.11
Plasma	0.381	0.076	5.01
WB	0.360	0.067	5.37
RBC	1.046	0.132	7.92
Plasma	1.479	0.204	7.25
WB	1.268	0.172	7.37
RBC	0.713	0.044	16.2
Plasma	1.065	0.097	11.0
WB	0.915	0.079	11.6
RBC	0.679	0.058	11.7
Plasma	1.173	0.104	11.3
WB	0.867	0.075	11.6
RBC	1.281	0.084	15.3
Plasma	2.166	0.156	13.9
WB	1.721	0.120	14.3

RBC = red blood cell component; WB = whole blood.

TABLE II
Hemodynamic Data in Chronic Anemia Experiments

	Control	Anemia
Heart rate per minute	71 (66-82)	111 (100-124) <i>P</i> < 0.01
Cardiac output, <i>ml/kg per min</i>	136 (112-167)	231 (203-265) <i>P</i> < 0.01
Stroke volume, <i>ml/kg per beat</i>	1.94 (1.77-2.16)	2.08 (2.02-2.14) NS
Mixed venous blood O ₂ , <i>% saturation</i>	70 (67-73)	38 (35-40) <i>P</i> < 0.01
Systemic O ₂ consumption, <i>ml/kg per min.</i>	5.6 (4.9-6.1)	6.0 (5.8-6.2) NS

Observations were made with the dogs lying at rest. Initial number is the average of four dogs (Nos. 4-7). Numbers in parentheses represent the range of mean values for separate dogs. *P* values indicate significance of difference from control (paired *t* test). NS = not significantly different.

observations was made before exercise with the dog standing at rest on the treadmill. Finally, exercise, performed for periods of 8 min with intervening rest periods of 5 min, consisted of running up a 10° grade at treadmill speeds ranging from 2 to 5 miles/hr. Aortic blood samples for lactate and pyruvate analyses were obtained at 4 min, cardiac output determined at 5 min, and blood samples for systemic (a-v)O₂ difference were obtained from 6 to 7 min of exercise.

Techniques

Simultaneous aortic and mixed venous blood samples for O₂ determinations were obtained from the catheters over 60- to 90-sec periods. The hemoglobin concentration was determined spectrophotometrically. In the chronic anemia experiments blood O₂ concentration was determined by the manometric method (15) and O₂ saturation was calculated. In the exercise experiments O₂ concentration was calculated from: blood Po₂ and pH (Radiometer Co., Copenhagen, Denmark), hemoglobin concentration, and an O₂ dissociation curve. Cardiac output was estimated by the dye dilution method by injecting 1 mg Indocyanine green into the pulmonary artery catheter and withdrawing blood from the aortic catheter through a GME densitometer. Systemic O₂ consumption rate was calculated from the product of cardiac output and systemic blood (a-v)O₂ difference. Blood samples for lactate and pyruvate were rapidly withdrawn from the aortic catheter into disposable syringes in a standardized manner, injected immediately into trichloroacetic acid at 0°C, and analyzed by modifications of the methods of Barker and Summerson and Friedemann and Haugen (16). Duplicate determinations checked within 2%.

If the L/P were higher in the plasma than in the red blood cells, the greater proportion of plasma in anemic blood would be expected to increase the L/P of whole blood, even if the plasma and red cell L/P each remained constant. To investigate this possible explanation for a rise in blood L/P during anemia, on five occasions freshly shed whole blood

TABLE III
Arterial Blood Lactate, Pyruvate, and L/P: Variation during Control and the Effect of Anemia

Dog	Condition	Lactate	Pyruvate	L/P
<i>mmole/liter</i>				
1	Control, n = 6	0.946 ± 0.611	0.169 ± 0.100	5.44 ± 0.69
	Anemia, n = 21	0.919 ± 0.277	0.151 ± 0.054	6.22 ± 0.68
		NS	NS	P < 0.05
2	Control, n = 7	0.393 ± 0.130	0.073 ± 0.024	5.14 ± 0.49
	Anemia, n = 14	0.765 ± 0.244	0.130 ± 0.046	5.95 ± 0.66
		P < 0.02	P < 0.02	P < 0.02
3	Control, n = 7	0.590 ± 0.308	0.107 ± 0.049	5.39 ± 0.53
	Anemia, n = 18	0.706 ± 0.187	0.123 ± 0.036	5.80 ± 0.68
		NS	NS	NS
4	Control, n = 39	1.415 ± 0.487	0.195 ± 0.039	7.10 ± 1.47
	Anemia, n = 25	1.394 ± 0.497	0.181 ± 0.051	7.50 ± 1.09
		NS	NS	NS
5	Control, n = 32	0.785 ± 0.276	0.130 ± 0.033	5.96 ± 0.89
	Anemia, n = 25	1.592 ± 1.072	0.181 ± 0.064	7.99 ± 2.54
		P < 0.001	P < 0.001	P < 0.001
6	Control, n = 34	1.025 ± 0.237	0.171 ± 0.050	5.88 ± 0.82
	Anemia, n = 30	1.158 ± 0.496	0.160 ± 0.041	6.98 ± 1.14
		NS	NS	P < 0.001
7	Control, n = 19	0.785 ± 0.223	0.140 ± 0.034	5.59 ± 0.81
	Anemia, n = 25	0.692 ± 0.237	0.104 ± 0.025	6.58 ± 0.84
		NS	P < 0.001	P < 0.001
8	Control, n = 7	0.903 ± 0.439	0.164 ± 0.072	5.42 ± 0.41
	*Control, n = 15	1.087 ± 0.230	0.200 ± 0.036	5.54 ± 0.54
		NS	NS	NS

n = number of observations. Values represent mean ± SD. Control data include observations before anemia and after recovery from anemia. Statistics calculated by nonpaired *t* test.

* Serial observations in dog No. 8 carried out over a period of time equal to that of the anemia period in the other dogs (5 wk).

was separated as rapidly as possible by centrifugation into two components: one containing mainly plasma and the other mainly red blood cells. An aliquot of the same blood sample was set aside for an equal time (4 min) without centrifugation. The results appear in Table I. The L/P was lowest in the plasma component, highest in the red cell component, and intermediate in whole blood, indicating that the higher proportion of plasma in anemic blood should slightly decrease, but not increase, the L/P of whole blood. These results confirm similar reported data (16).

RESULTS

Chronic anemia. All observations were made with the dogs lying at rest. Control and anemia hemodynamic data were obtained in four dogs (Table II). Heart rate and cardiac output increased, and mixed venous blood O₂ saturation decreased during anemia. The slight increases in stroke volume and systemic O₂ consumption were not statistically significant. These variables returned to the initial control levels after the dogs recovered from the anemia.

Arterial blood lactate and pyruvate data for all eight dogs are presented in Table III. Control lactate and pyruvate concentrations in each dog varied greatly from

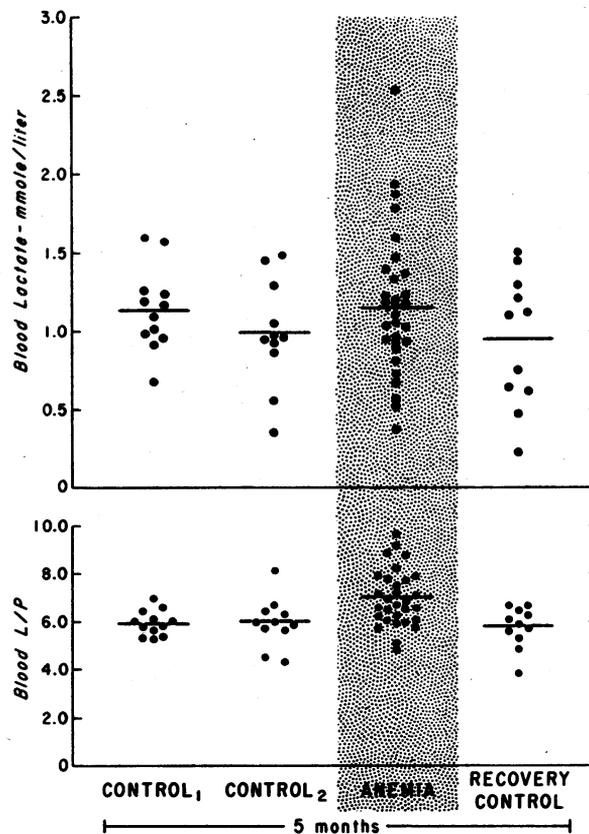


FIGURE 1 The variability of blood lactate and L/P in dog No. 6 during 5 months. Dots represent values on separate days, and the horizontal lines represent means for each period indicated. Blood lactate concentration fluctuated widely but was not significantly affected by anemia (shaded area). Blood L/P varied less and increased during anemia ($P < 0.001$).

day to day, and the mean control values differed from dog to dog. Blood L/P was more constant, mean values in all but one dog falling between 5.14 and 5.96. The coefficients of variation (SD/mean) for control values for all dogs were: lactate 40%, pyruvate 35%, and L/P 13%.

There were significant ($P < 0.05$) increases in arterial blood L/P during anemia in five of seven dogs. In the other two, smaller increases in L/P were not significant. Although significant changes in blood lactate and pyruvate concentrations occurred during anemia in a few instances, the directions of these changes were inconsistent between different dogs. Therefore, the increase in L/P did not depend upon any specific changes in either lactate or pyruvate concentration. There were no significant changes in lactate, pyruvate, or L/P in dog No. 8, which was not made anemic.

The comparison between changes in arterial blood lactate and L/P is illustrated in Fig. 1 for dog No. 6,

TABLE IV
Hemodynamic Data in Exercise Experiments

	Control (rest, lying)	Standing rest	Maximum exercise
Heart rate per minute	60 (52-70)	88 (74-103) <i>P</i> < 0.01	176 (155-208) <i>P</i> < 0.01
Cardiac output, ml/kg per min	115 (96-138)	147 (122-169) <i>P</i> < 0.02	356 (294-450) <i>P</i> < 0.01
Stroke volume, ml/kg per beat	1.91 (1.66-2.38)	1.70 (1.43-2.25) <i>P</i> < 0.05	2.01 (1.88-2.16) NS
Mixed venous blood O ₂ , % saturation	69 (62-78)	60 (48-71) <i>P</i> < 0.02	37 (30-49) <i>P</i> < 0.01
Systemic O ₂ consumption, ml/kg per min	6.1 (5.6-7.0)	10.3 (9.0-11.5) <i>P</i> < 0.01	45.8 (28.3-66.5) <i>P</i> < 0.01

Initial number is the average of four dogs. Numbers in parentheses represent the range of separate mean values for the different dogs, except for "maximum exercise," where numbers represent observations during maximum level of exercise for each dog. Statistics as in Table II.

in which observations extended for 5 months. The daily variability in lactate concentration was relatively great, and the differences between the values during the initial two control periods, the anemia period, and the final recovery control period, were not significant. For L/P, the daily variability was less. Moreover, the L/P values for the initial two control and recovery periods were comparable, and they differed significantly from the anemia values (*P* < 0.001).

While anemic, the dogs were less eager to run but otherwise remained healthy. While resting observations

were being made, their behavior was the same as that during the control period. After the dogs recovered from the anemia, their original vigor returned.

Exercise. Rest and exercise hemodynamic data for dog Nos. 9-12 when they were not anemic are given in Table IV. Fig. 2 shows the relationship between cardiac output and systemic O₂ consumption by the tissues. This relationship did not appear to be entirely uniform in the different dogs, i.e., cardiac output was relatively high in dog No. 10 (square symbols) and low in dog No. 9 (circle symbols). Mean arterial blood pH was

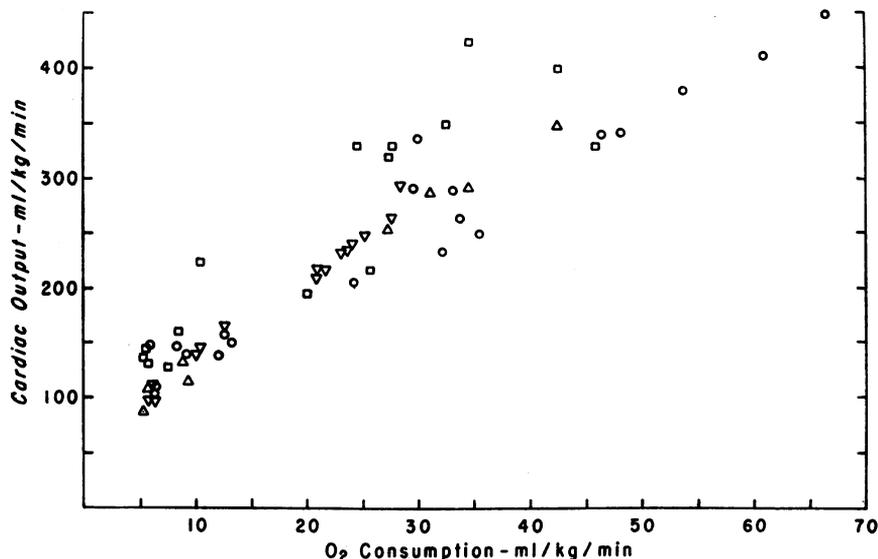


FIGURE 2 The relationship between cardiac output and systemic O₂ consumption when the dogs were not anemic. Resting observations are to the left and exercise observations extend to the right. (○ = dog No. 9, □ = dog No. 10, △ = dog No. 11, ▽ = dog No. 12.)

7.40 lying at rest, 7.43 standing at rest, and during exercise reached maximum values ranging from 7.44 to 7.51 in the four dogs.

Changes in arterial blood L/P during exercise are shown in Fig. 3. Data obtained when dogs were not anemic, represented by open symbols, differed in separate dogs. In two dogs (No. 11 and No. 12, Fig. 3, lower panels), L/P consistently increased during exercise which was strenuous enough to increase systemic O₂ consumption by four to five times the resting level. In dog No. 9 (upper left panel), L/P did not increase until O₂ consumption reached 8–10 times the resting level, and in dog No. 10 (upper right panel), L/P consistently decreased during exercise when he was not anemic. To determine the effect of restriction in the supply of O₂ to tissues while their O₂ consumption was acutely increased, we repeated the exercise studies at four levels of anemia, with hemoglobin concentrations of approximately 8, 6, 4, and 2.5 g/100 ml. The results during anemia are represented in Fig. 3 by solid symbols (two dogs would not run on the treadmill at the most severe anemia level). Irrespective of their differ-

ences when not anemic, as the dog's ability to augment acutely tissue O₂ supply was restricted by increasingly severe anemia, progressively larger increases in blood L/P appeared during exercise at progressively lower rates of O₂ consumption. Moreover, the dogs whose L/P increased most readily when they were not anemic had the most pronounced effect from anemia.

Corresponding changes in mixed venous blood Po₂ are shown in Fig. 4. Anemia decreased the venous blood Po₂ at all levels of systemic O₂ consumption during rest and exercise, and the magnitude of the decrease in Po₂ was proportional to the degree of anemia. In the presence of severe anemia, mixed venous blood Po₂ fell during exercise to as low as 12 mm Hg (11–12% O₂ saturation) in three dogs.

DISCUSSION

Huckabee showed that moment-to-moment changes in blood lactate and pyruvate concentrations occurred for no apparent reason or could be readily induced by a variety of factors, many of which were unrelated to O₂ supply (17). Blood L/P, however, remained nearly

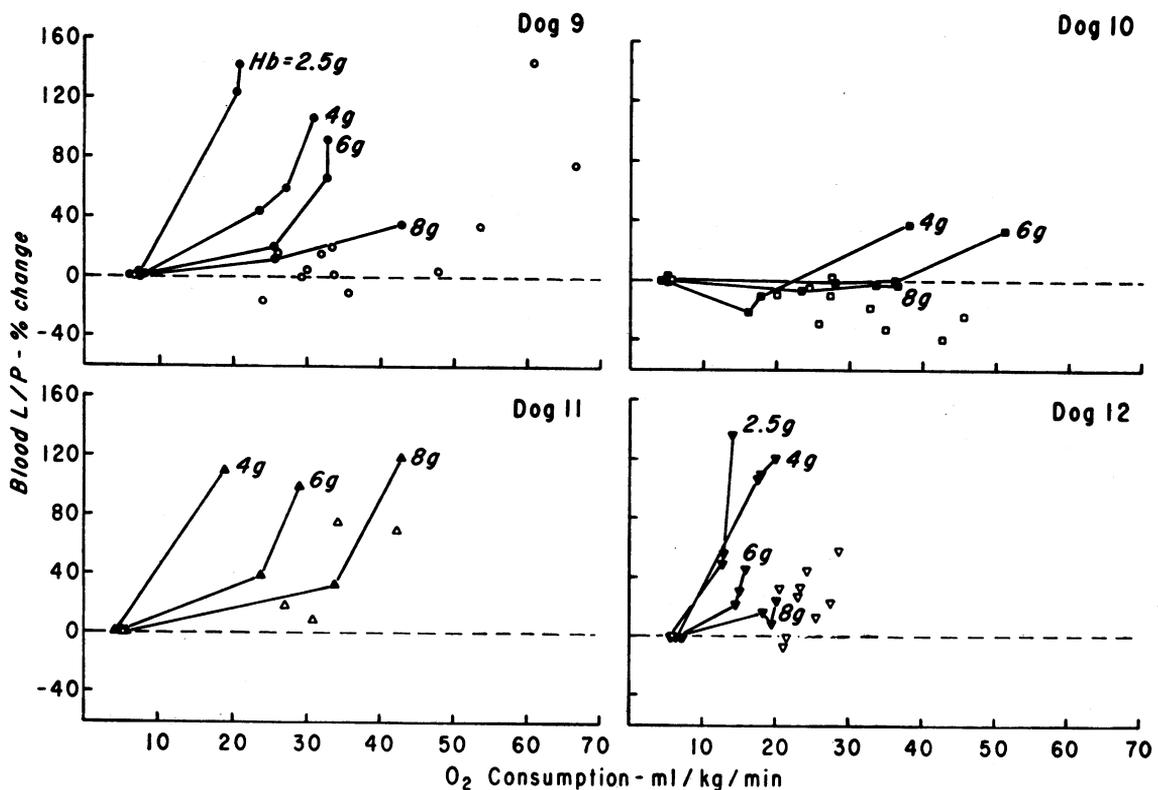


FIGURE 3 Per cent changes in arterial blood L/P related to changes in systemic O₂ consumption during muscular exercise. Each panel represents a separate dog. Open symbols are observations made when the dogs were not anemic; solid symbols, observations during anemia. There were four levels of anemia (Hb = 8, 6, 4, and 2.5 g), and the lines join observations made at each different level.

constant as long as O_2 supply was not changed. In our experiments, repeated determinations of blood lactate and pyruvate concentrations during the control period establish the range of fluctuations in these substrates and in blood L/P which normally occur, not acutely as previously studied, but sporadically from day to day over an extended period. It is worth emphasizing the basal state of these dogs. From external appearances they always appeared relaxed. As evidence, their heart rates and systemic O_2 consumption values (Table II) were consistent from day to day (mean day-to-day variation of each, 12%) and lower than most values previously reported for awake dogs (18-21). Under these conditions, their blood lactate and pyruvate concentrations varied over a wide range while L/P remained relatively constant. Thus, variations in unidentified factors which do not appear to be related to O_2 supply vigorously influenced lactate and pyruvate concentrations but had little effect on blood L/P.

In view of their marked fluctuations even during the control period when we attempted to keep the condition of the dogs stable, it is not surprising to find changes in the blood concentrations of both lactate and pyruvate when the dogs were made anemic. In some instances

these changes were statistically significant; their direction, however, was completely inconsistent in different dogs. Thus, whatever effect anemia itself may have had on the blood concentrations of these substrates, it was largely overshadowed by other unidentified factors, perhaps by the same ones responsible for the fluctuations in control lactate and pyruvate concentrations. With blood L/P, the result differed. Although blood L/P on some days during anemia equaled the control values, other anemia values were clearly above the previously established control range (e.g. Fig. 1), and the direction of change in mean L/P during anemia was consistently upwards. One possibility is that anemia regularly increased the L/P; another is that anemia made the animal more susceptible to other factors influencing L/P which were inconstantly present. The overlap between control and anemia L/P values provides an explanation for the previous inconsistent reports of the effect of chronic hypoxemia or anemia on blood L/P (8-13). With enough observations, however, the effect of anemia on blood L/P is specific enough to be detected even in the presence of variables in addition to O_2 supply which may slightly influence day-to-day blood L/P values. We have no proof that tissue hypoxia was the

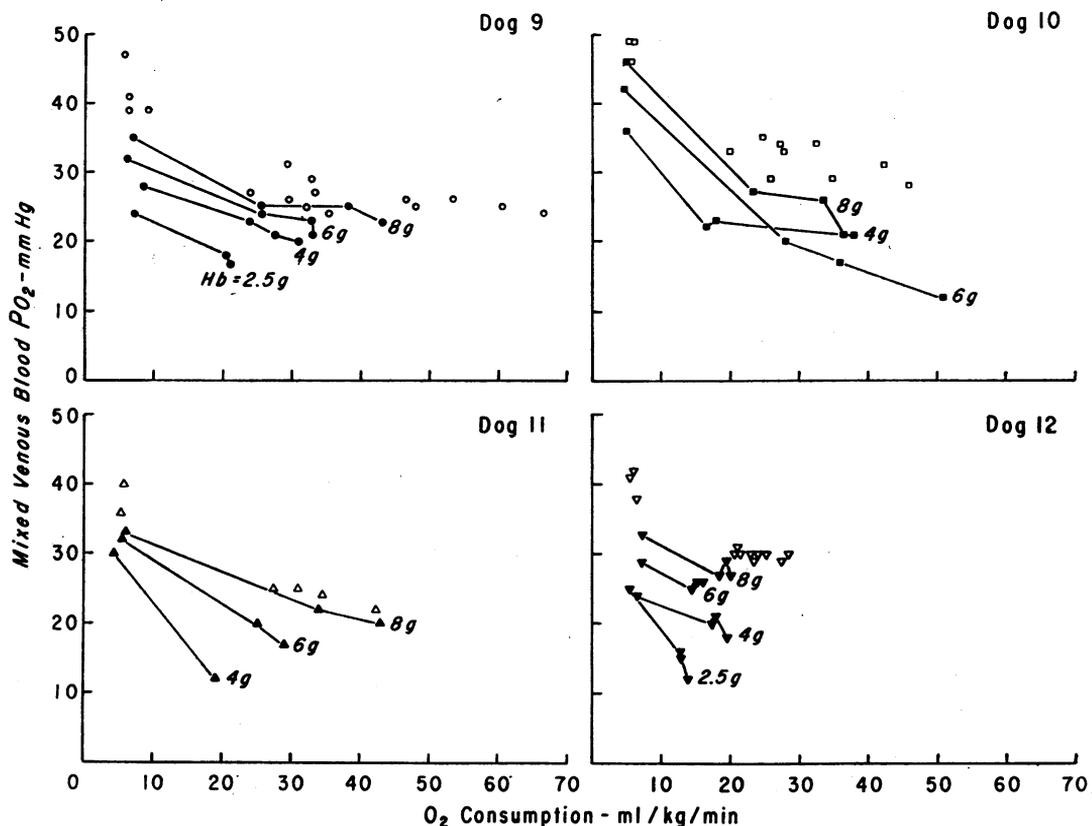


FIGURE 4 Mixed venous blood PO_2 during rest and exercise. Explanation as for Fig. 3.

specific feature of anemia responsible for the increased blood L/P, but it seems the most plausible explanation. These findings coincide with Huckabee's conclusion from his acute experiments that blood L/P, rather than lactate or pyruvate concentration, is regularly affected by changes in O₂ supply.

We would not expect the circulatory adjustments during anemia to be uniform throughout the body; therefore, neither would we anticipate that hypoxia was evenly distributed among different tissues. The lactate and pyruvate concentrations in arterial blood represent a mixture of the concentrations in venous blood draining the different body tissues. Thus, from the increase in arterial blood L/P, we have no information regarding the distribution of tissue hypoxia in anemia, nor can we distinguish diffuse from focal tissue hypoxia.

Normally, an acute increase in the rate of O₂ consumption by tissue is compensated, at least partly, by a simultaneous increase in O₂ delivery via increased blood flow to the tissue. Since O₂ delivery is augmented, the increase in O₂ consumption might not result in tissue hypoxia. Nevertheless, arterial blood L/P increases during mild muscular exercise in normal but sedentary humans (22-24), which suggests that O₂ availability for metabolism in the tissues is not maintained at a constant level in these subjects even when O₂ consumption is only modestly increased. Among subjects who regularly engage in vigorous physical activity, the increase in arterial blood L/P is considerably less (25, 26). In certain pathologic conditions, the capacity for acute increase in tissue O₂ delivery is impaired by limited blood flow. In some patients, heart disease limits the capacity for increased systemic blood flow; in others, narrowed arteries interfere with blood flow locally. Under these conditions, acute increase in O₂ consumption by the potentially ischemic tissue is accompanied by an exceptionally large increase in blood L/P: either the local venous blood in local ischemia, e.g., myocardium (27) or leg (28, 29); or the arterial blood in systemic ischemia, e.g., cardiac failure (22, 30). The explanation which has been given for the exceptional increases in blood L/P is that when the increase in blood flow in response to increased O₂ consumption is less than normal, the fall in O₂ availability for metabolism is greater, i.e., more marked tissue hypoxia occurs.

The purpose of the exercise experiments in the dogs is to examine the significance of blood L/P changes which accompany increased O₂ consumption in tissue under somewhat different experimental conditions. In each of the dogs we studied, when he was not anemic, the increase in arterial blood L/P during exercise was substantially less than that reported for sedentary humans, even though the degree of exercise as judged by increase in O₂ consumption rate was greater in the

dogs. In fact, in two dogs the L/P did not regularly increase even when systemic O₂ consumption reached seven times the resting level. These results suggest that tissue O₂ supply is better maintained during exercise in dogs than in most humans, perhaps due to species differences or to differences in physical activity. Cardiac output is one factor governing tissue O₂ supply, and there is evidence that cardiac output relative to O₂ consumption is higher during exercise in dogs (Fig. 2 and references 18 and 19) than in humans (31-34). Thus, the more stable blood L/P in the dog can be explained partly by superior tissue O₂ supply due to higher cardiac output.

Anemia in the dogs limited the extent to which they could augment O₂ delivery to their tissues during exercise. In these experiments, O₂ delivery was limited not by ischemia but by low blood O₂ concentration. The presence of anemia enhanced the increase in blood L/P during exercise, and this effect of anemia was proportional to its severity. The more that augmented O₂ delivery was inhibited, the greater the increase in blood L/P for any level of systemic O₂ consumption (Fig. 3). These experiments show that exercise changes in blood L/P are responsive in a predictable manner to concurrent alterations in tissue O₂ supply; therefore, the changes in blood L/P appear to be related to changes in the availability of O₂ to the respiratory enzyme system in the tissue rather than to some other effect of exercise. The results of these experiments also substantiate the interpretation presented in the previous studies of patients with ischemic disease that their exceptionally large increases in blood L/P were due to tissue hypoxia.

ACKNOWLEDGMENTS

John Oxendine, Stephen Moore, Sandra Hora, and Marilyn Paul provided vital technical help. The blood O₂ dissociation curves were determined by members of Dr. James Metcalfe's laboratory. The authors are grateful to Dr. Richard L. Dobson, who critically reviewed the manuscript.

This work was supported by Public Health Service Grant HE 10433.

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