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OXYGEN DEFICIT INCURRED DURING HYPOXIA AND ITS RELATION TO EXCESS LACTATE

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FOREWORD

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The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

This report has been reviewed and is approved.

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ABSTRACT

The oxygen deficit incurred during hypoxia was compared to the peak excess lactate (XL) level in order to see if any consistent relationship existed when a known oxygen limitation was imposed. Twelve anesthetized dogs, in which ventilation was held constant, breathed 9.1% O_2 in N_2 for 10, 20, and 30 minutes. Oxygen uptake was measured every 10 minutes during a control period, hypoxia, and a recovery period. Oxygen content and tension of systemic and pulmonary arterial blood were measured at the end of each of these periods. Excess lactate was calculated from blood lactate and pyruvate levels measured during the control period, the last minute of hypoxia, the first minute of recovery, and at intervals thereafter. Depletion and repletion of oxygen stores were estimated by assuming values on a body-weight basis for functional residual volume, body water, total blood volume, and its distribution. "True" O_2 deficit and "true" excess O_2 of recovery were thus calculated and compared to each other and to peak XL values. Excess O_2 uptake measured during recovery, which is the oxygen debt as usually measured, never was as great as the oxygen deficit incurred during hypoxia, and bore little consistent relationship to peak XL. The "true" O_2 deficit, on the other hand, had a coefficient of correlation of .781 when compared with peak XL.

OXYGEN DEFICIT INCURRED DURING HYPOXIA AND ITS RELATION TO EXCESS LACTATE

I. INTRODUCTION

Although there have been many reports in which excess lactate has been compared with the excess oxygen uptake measured during recovery from exercise (11, 18-20), a straightforward comparison between excess lactate and the oxygen deficit incurred during brief exposure to low inspired oxygen tensions has apparently not been made. The great variability shown in ratios of oxygen repayment to oxygen deficit during exercise (12) casts some doubt on what debt is actually being repaid. The classical concept has been that at least a certain portion of the excess oxygen uptake after exercise is used to reconvert lactate formed anaerobically during exercise. Even this has been challenged by Alpert (1). More recently, it has been shown that exercising muscle may be taking up lactate rather than producing it (17). With the additional knowledge that other rate-limiting factors besides oxygen supply in the respiratory chain can result in lactate formation (10), there is ample reason to suspect that "oxygen debt" of exercise, as it is conventionally measured, and excess lactate need not have any consistent relation to each other, causal or otherwise. Such comparisons, therefore, shed no light on what relationship excess lactate may bear to metabolism when it is limited by the oxygen supply. The measurement of oxygen deficit during hypoxia was chosen to compare with excess lactate in these studies with the idea of seeing if any consistent relationship did exist when a known oxygen limitation was imposed. In so doing, the realization developed that both oxygen deficit and oxygen debt or repayment are a chimera because of the lack of valid evidence for the correctness of the basic assumptions necessary to their measurement and the lack of knowledge about the actual energy deficit which they imply. Some of these difficulties will be illustrated.

II. METHODS AND PROCEDURES

Twelve dogs, ranging in weight from 17.0 to 26.8 kg. (average, 20.5 kg.), were anesthetized with 0.6 ml. kg. Dial with urethan given intraperitoneally. The trachea was cannulated and catheters were placed in both femoral arteries, a femoral vein, and a pulmonary artery. Systemic arterial pressure was monitored continuously by a suitable transducer and recorder. To insure complete relaxation of the animal, 30 mg. of succinylcholine chloride were injected intramuscularly and 0.1 mg./min. in saline was infused continuously into the femoral vein. The tracheal cannula was then connected to a Harvard animal respirator and the tidal volume was set so that, at a rate between 10 to 15 breaths per minute, the end-tidal P_{CO_2} as measured by a Beckman LB-1 CO_2 analyzer was approximately 35 mm. Hg. Once this had been achieved, the end-tidal P_{CO_2} sampling was discontinued and the setting of the pump was not altered.

Two hours elapsed between the time anesthetic was given and the beginning of the experiment. During that time, the level of anesthesia became very even, as judged by the eyelid reflex, and remained at an even level throughout the experiment. After initially flushing expired gas through the collecting system, 10-minute samples of expired gas were collected in Douglas bags according to the

schedule shown in table I. The dry fractional content of CO_2 and O_2 in the bag was analyzed (Beckman LB-1 and E-2 gas analyzers), and the volume of the bag was measured by squeezing the contents through a dry test meter. To that volume was added the volume used for analyzing the gas. After correction of the volume to standard conditions, minute volume of ventilation, oxygen uptake, and CO_2 output were calculated.

During the hypoxia periods shown in table I, the inspired gas line was connected to a demand regulator on a high-pressure cylinder containing 9.14% O_2 in N_2. The respirator and gas lines were checked periodically for leaks by connecting nitrogen to the inspired line, substituting a small rubber bag for the animal, and measuring the O_2 in the Douglas bag collected after a suitable washout period. No leaks of outside air into the system were ever detected.

Systemic arterial blood and mixed venous blood were sampled simultaneously at the times shown in table I. Oxygen tension was measured in all by an O_2 electrode in a water bath (Instrumentation Laboratory, Inc., model 113) set to the rectal temperature of the animal at the time of sampling. In addition, arterial P_{CO_2} and pH were measured by appropriate electrodes in those samples taken during the control periods. The total volume of blood taken in each syringe was 3 ml., except in the case of control period arterial samples which were 6 ml. Oxygen content of all were measured spectrophotometrically (16).

Arterial blood was also sampled directly into a 3-ml. pipet at the times indicated in table I. Transfer to cold trichloroacetic acid (10% w/v) was accomplished within 30 seconds, and the deproteinized filtrates were analyzed for lactate (5) and pyruvate (7). Results were expressed as millimoles per liter of blood. Excess lactate (XL) was calculated as:

$$XL = Ln - Pn\ (Lo/Po)$$

where L and P are lactacte and pyruvate, respectively; n and o are experimental and control values. Control values of Lo/Po were taken as the average of two measurements made before hypoxic period.

Although more than 130 ml. of blood were taken from each animal, the loss was evenly distributed over a 5-hour period. During this time, the succinylcholine infusion amounted to

TABLE I

Time (in minutes) in the experiment at which gas and blood samples were taken

Experimental period	Douglas bag collection	Pipet blood sampling*	Syringe blood sampling†
Control I	0 – 10	5	
	10 – 20	15	18
Hypoxia I	20 – 30	30	28
Recovery I	30 – 40	31, 35	
	40 – 50	40	
	50 – 60	60	55
Control II	90 – 100	95	
	100 – 110	105	108
Hypoxia II	110 – 120		
	120 – 130	130	128
Recovery II	130 – 140	131, 135	
	140 – 150	140	
	150 – 160	160	155
	160 – 170		
Control III	190 – 200	195	
	200 – 210	205	208
Hypoxia III	210 – 220		
	220 – 230		
	230 – 240	240	238
Recovery III	240 – 250	241, 245	
	250 – 260	250	
	260 – 270	270	265
	270 – 280		
	280 – 290		

*Pipet samples of arterial blood were used for analysis of lactate and pyruvate.

†Oxygen tension and content were measured in blood drawn simultaneously into syringes from femoral and pulmonary arteries.

approximately 290 ml. of saline. When the large size of the animals which were used is also considered, it seems unlikely that the blood sampling alone created any problem. Hematocrit measurements on each arterial blood sample showed no significant changes with time except for temporary elevation during hypoxic periods.

Changes in oxygen stores

External dead space of connecting tubing and stopcock was 560 ml. STPD. To this was added the stroke volume of the respiratory pump, which was recorded for each animal. When the inhaled gas mixture was changed between room air and 9.14% O_2, that portion of the apparent change in O_2 uptake which was accounted for by change in O_2 content in the external dead space was calculated as:

$$(.209 - .091) \times (560 + \text{stroke vol.}) = \text{ml. } O_2 \text{ STPD.}$$

In order to calculate the change in lung O_2 stores, it was assumed that the end-expiratory lung volume of the dog was 24 ml. STPD/kg. body weight and that the difference in arterial P_{O_2} was identical to the change in alveolar P_{O_2} when the inhaled mixture was altered. This involved the further assumption that the gaseous composition of the estimated lung volume was largely alveolar in nature.

$$\frac{(Pa_{O_2})C \text{ or } R - (Pa_{O_2})H}{P_B - P_{H_2O}} \times 24 \times \text{body wt.} = \text{ml. } O_2 \text{ STPD}$$

where C is control, R is recovery, and H is hypoxia.

The changes of oxygen in solution in body water were calculated by assuming that there were 600 ml. body water/kg. body weight and that the change in mixed venous P_{O_2} was the same as the change in mean tissue P_{O_2}.

$$\frac{(P\bar{v}_{O_2})C \text{ or } R - (P\bar{v}_{O_2})H}{760} \times 600 \times \text{body wt.} \times .0214 = \text{ml. } O_2 \text{ STPD}$$

where .0214 is the Bunsen solubility coefficient for plasma at 38° C.

The estimate of changes in blood O_2 stores was based on the assumption that one-third of the total blood volume was arterial and two-thirds was venous. Total blood volume was assumed to be 90 ml./kg. body weight. The O_2 content of arterial and mixed venous blood was measured during each period, and the change in content was used to calculate the total amount of unloading or loading of oxygen in blood with change of inhaled oxygen mixture.

The sum of the above for each hypoxic and recovery period for each animal was subtracted from the total oxygen deficit during hypoxia or from the excess oxygen of recovery.

Oxygen deficit and excess oxygen of recovery

The basic assumption was made that, during the hypoxic period, the tissue demand for oxygen would have continued at the level measured during the control period if availability had not been limited. Integration of the area enclosed by the control $\dot{V}_{O_2}$ and the actually measured $\dot{V}_{O_2}$ for the time of hypoxia was taken to be the total apparent O_2 deficit. In order to obtain the "true" O_2 deficit, the total change in O_2 stores for this period was subtracted and the result expressed as milliliters O_2 STPD per kilogram body weight.

Similarly, the increase in $\dot{V}_{O_2}$ above control level during recovery was summed over the time it took for $\dot{V}_{O_2}$ to return within 5% of the control $\dot{V}_{O_2}$. This was an arbitrary criterion based on the maximum error possible in the measurement of $\dot{V}_{O_2}$. The change in O_2 stores with reoxygenation was subtracted from the total apparent excess oxygen of recovery to find the "true" excess oxygen of recovery.

III. RESULTS

In table II, values of arterial and mixed venous P_{O_2} during hypoxic periods were below the "critical P_{O_2}" previously reported for the appearance of excess lactate (3). Arterial control values were similar throughout the experiment, but mixed venous P_{O_2} tended to decline with time. The decline was attributable to that shown in cardiac output, which gradually falls with time in the anesthetized dog (9).

TABLE II

Mean values of blood gas tensions, pH, and cardiac output

Period	$P_{a_{O_2}}$ (mm. Hg)	$P_{v_{O_2}}$ (mm. Hg)	$\dot{Q}$ (ml./kg.-min)	$P_{a_{CO_2}}$ (mm. Hg)	pHa
Control I	88.3 ± 2.5*	47.2 ± 1.5	111 ± 11	37.9 ± 1.0	7.32 ± .01
Hypoxia I	27.3 ± .8	19.5 ± .8			
Recovery I	82.0 ± 3.5	44.3 ± 1.6			
Control II	87.8 ± 1.7	44.3 ± 1.3	95 ± 7	36.2 ± .5	7.33 ± .01
Hypoxia II	24.5 ± .9	15.8 ± .9			
Recovery II	84.8 ± 2.0	41.9 ± 1.2			
Control III	89.1 ± 2.2	42.3 ± 1.8	87 ± 10	36.9 ± 1.1	7.34 ± .01
Hypoxia III	24.4 ± 1.2	14.3 ± .9			
Recovery III	84.5 ± 1.7	41.4 ± 1.6			

*$\bar{X}$ ± S.E. (mean ± standard error of mean).

Average measured values of oxygen uptake during control periods were not significantly different with time (fig. 1). A sharp decrease was noted in every case upon exposure to low oxygen. In every recovery period, oxygen uptake was well above control values and gradually returned to that level. The "repayment" period of excess oxygen uptake was roughly proportional to the length of the hypoxia period. In the first 10 minutes of hypoxia, oxygen uptake was always lower than in succeeding 10-minute segments and was of approximately the same magnitude in all three hypoxic periods. In the second and third hypoxic periods (20 and 30 minutes, respectively), oxygen uptake returned to an intermediate level which was evidently a new equilibrium, since there was no significant difference in the second and third 10-minute samples taken during the 30-minute hypoxic period. When the mean oxygen uptake measured in the second 10-minute sample was compared for hypoxic periods II and III, these did not differ significantly.

With the exception of one animal, excess lactate was present in arterial blood at the end of every hypoxic period. Peak excess lactate most often occurred in the sample taken 1 minute after inhaled gas was changed back to room air (24 of 36 sets of measurements). The ratios of lactate to pyruvate were approximately equal at 0 and 1 minute into the recovery period, diminishing rapidly thereafter.

The average calculated depletion of oxygen stores which took place during inhalation of the low oxygen mixture was 18.3 ml./kg. body weight. This was not significantly affected by the length of the hypoxic period. The average repletion of oxygen stores during recovery on room air was 17.1 ml./kg., and this was not significantly different from the average depletion. The compartmental changes in O_2 stores in table III indicate that the change in blood O_2 stores accounted for over half the total estimated change. Once stroke volume of the respiratory pump had been set for each animal, the external dead space was fixed and its residual O_2 accounted for slightly more than one-fourth the total. Lung and water stores were about one-eighth and one-thirty-second, respectively.

The estimated change in O_2 stores during hypoxia was subtracted from the total oxygen deficit in order to arrive at a "true" O_2 deficit. In figure 2 the individual values were plotted against the corresponding peak excess lactate measured during that period. The equation

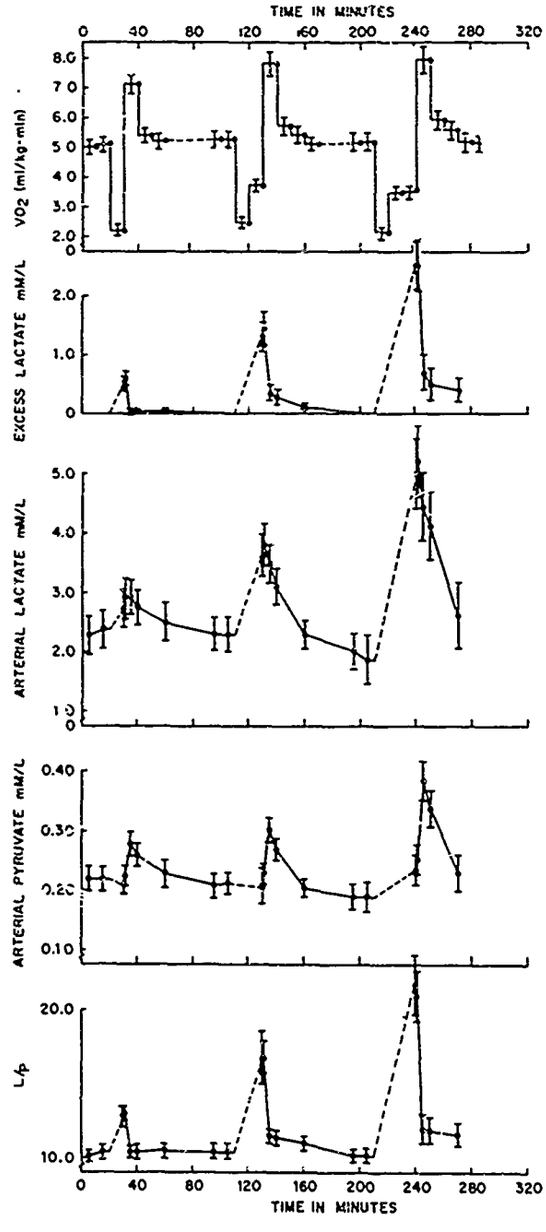

FIGURE 1

Mean values of oxygen uptake ($\dot{V}O_2$), excess lactate, arterial lactate, arterial pyruvate, and the lactate-pyruvate ratio (L/P) for 12 animals. Vertical bars are ± 1 S.E. of the mean. Hypoxic periods were 20 to 30, 110 to 130, and 210 to 240 minutes.

for the regression line, calculated by the method of least squares, was XL = 0.11 + 0.053 "true" O_2 deficit. The coefficient of correlation was .781.

The peak increase in lactate above the control level at the end of the hypoxic period is shown in relation to the "true" O_2 deficit in figure 3. The coefficient of correlation, which was .833, was somewhat higher than it was in the case of excess lactate and the intercept on the ordinate was practically zero. Because ventilation was not permitted to increase, hypocapnia was largely prevented so that hypocapnic lactate production (4) was minimal. Of the peak increase in lactate, 87% was accounted for as excess lactate. In view of the usual hyperventilation and consequent hypocapnia that accompanies hypoxia, it seems unlikely that the same high correlation of lactate and O_2 deficit would be obtained if ventilation was not controlled.

The "true" excess O_2 of recovery was obtained by subtracting the change in O_2 stores which took place when the animal again breathed room air from the total excess O_2 uptake measured during recovery. This was plotted against the "true" O_2 deficit in figure 4. The line is that of identity, and all points fell below that line. In these experiments and by the specific criteria applied herewith, hypoxic O_2 debt was never fully repaid.

In figure 5, the "true" excess O_2 of recovery bore little relation to peak values of excess lactate.

IV. DISCUSSION

Although excess lactate did not correlate perfectly with the estimated "true" O_2 deficit, the correlation was sufficiently good to make excess lactate useful as a functional measure of hypoxia which is severe enough to limit metabolic uptake of oxygen. Since neither measurement can stand as an absolute measure, some question can be raised as to which should be taken as the standard for comparison. Another peculiar question is whether it is a justifiable assumption that the level of O_2 uptake would have continued at the control level if it had not been limited by availability.

TABLE III

Estimates (ml./kg.) of changes O_2 stores during hypoxia and recovery

Period	External dead space	Lung	Body water	Blood	Total
Hypoxia I	4.86 ± 16*	2.11 ± .08	0.46 ± .03	10.46 ± .68	17.89 ± .73
Hypoxia II	4.86 ± .16	2.19 ± .06	0.48 ± .02	10.82 ± .52	18.36 ± .49
Hypoxia III	4.86 ± .16	2.23 ± .09	0.49 ± .04	11.08 ± .68	18.66 ± .70
Recovery I	4.86 ± .16	1.89 ± .12	0.42 ± .03	9.21 ± .64	16.47 ± .69
Recovery II	4.86 ± .16	2.08 ± .06	0.45 ± .03	10.25 ± .62	16.12 ± 1.57
Recovery III	4.86 ± .16	2.07 ± .06	0.46 ± .03	9.94 ± .81	17.32 ± .80

*$\bar{X}$ ± S.E. (mean ± standard error of mean).

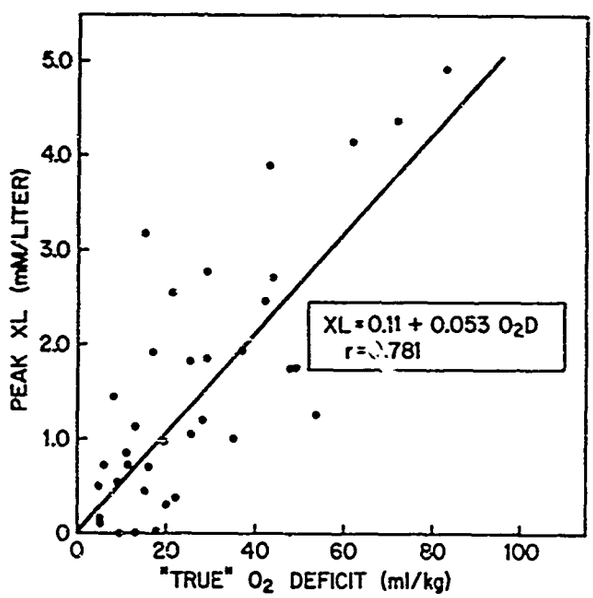

FIGURE 2

The relationship of the "true" O_2 deficit (O_2D) to the peak excess lactate value (XL) obtained for that period of hypoxia. Equation of the line was obtained by the method of least squares. There were three points for each animal.

A satisfactory answer cannot be given to either question. To take the latter one first, there was no extra demand for oxygen during hypoxia because of extra work of breathing in these experiments Poyart and Nahas (14) have recently shown, however, that oxygen uptake was increased as much as 30% in anesthetized dogs receiving catecholamine by infusion. The extent of catecholamine secretion during the hypoxic stress in these experiments is unknown, but the arterial blood pressure rose markedly in each animal during hypoxia. If O_2 demand was elevated by liberation or secretion of catecholamines during hypoxia, then the measured O_2 deficit represents an underestimate.

The several assumptions necessary to estimate the change in O_2 stores create considerable doubt about how truly O_2 deficit can be stated. The measurement of external dead space and its share in O_2 stores was straightforward. In order to estimate the change in O_2 stores, it was necessary to use a factor for the functional residual capacity. The chosen factor of 24 ml./kg. body weight was based on normal figures for man. In a series of 8 anesthetized, curarized dogs, Fenn et al. (6) obtained an average figure of 18.3 ml./kg. Based on nitrogen washout of the fastest compartment only, the data of Rossing (15) indicated a functional residual capacity of approximately 38 ml./kg. This is probably an underestimate in that the slowest compartment to wash out in his experiments probably was still lung nitrogen space, primarily. If these factors are used with the average decrease in arterial P_{O_2} during the first hypoxic period, the calculated change in lung O_2 stores becomes either 1.6 or 3.3 ml./kg. instead of 2.1 ml./kg. and would represent a 7% maximum deviation from the total change in O_2 stores which was shown in table III.

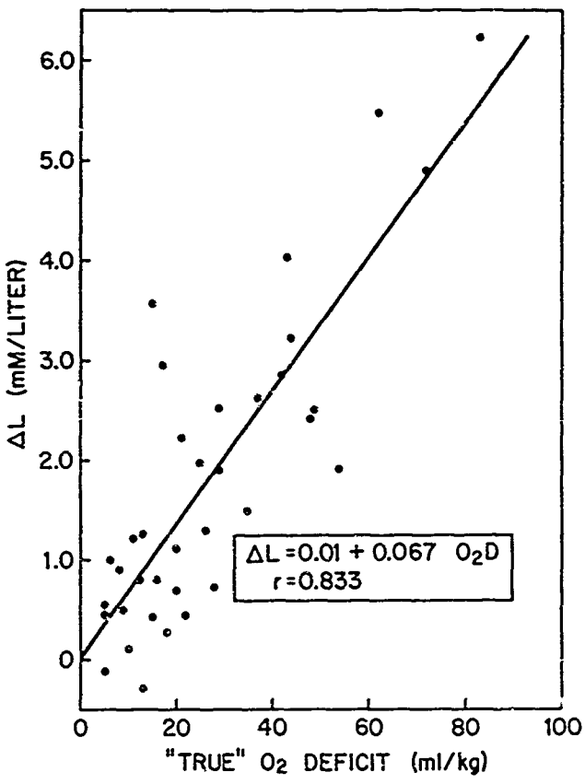

FIGURE 3

The relationship of the "true" O_2 deficit (O_2D) to the maximum increase in arterial lactate level above the control value (ΔL). There were three points for each animal.

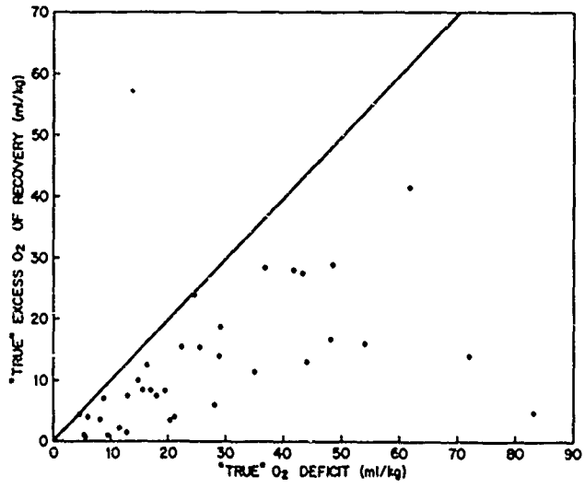

FIGURE 4

The relationship of the "true" O_2 deficit to the "true" excess O_2 uptake during recovery. The line was drawn through the identical values for both. Three points were obtained for each animal.

The changes in O_2 stores dissolved in body water are so little that large errors in any of the estimating factors would not have a large effect on the total change in O_2 stores. For example, if the change in tissue Po_2, which was taken to be that measured in mixed venous blood, were actually half the assumed value, the total change in O_2 stores would be altered by only 1%.

By far the greatest portion of the O_2 stores was that in blood. To obtain the blood volume, an average of several values for the dog, reported on the basis of body weight, was used (8). For any particular animal at any given time in the experiment, this factor could have differed considerably from the one used, 90 ml./kg. The range of values reported was from 64 to 135 ml./kg.; thus the calculated change in blood O_2 stores may have been in error by more than 30%. Furthermore, there is no way of knowing how much of the blood is arterial in nature and how much is venous. The proportion of two-thirds venous and one-third arterial blood was based on an approximate estimate of distribution in the vascular bed of man (2). It would be impossible to

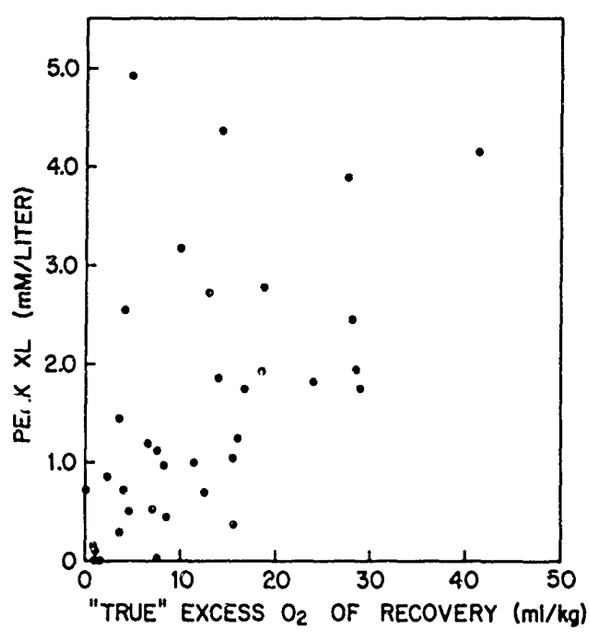

FIGURE 5

The peak excess lactate level for a particular hypoxic period in relation to the "true" excess oxygen uptake measured during recovery from that period.

judge the possible error incurred by this assumption. The actual changes in arterial and mixed venous O_2 contents during any period differed by no more than 2.5 volumes per 100 ml. of blood, so that a different proportion of arterial and mixed venous blood would probably not make a very large difference in the calculated total change of O_2 stores.

Because of the uncertainties associated with the calculated estimate of oxygen stores, another method based on a different set of assumptions was tried. In figure 1, it seemed evident in the second and third hypoxic periods that a new level of oxygen uptake was reached after 10 minutes of hypoxia. Every animal displayed the same pattern of response in O_2 uptake as that shown for the average in figure 1. The new level of O_2 uptake during hypoxia was taken to be a steady-state value. The much lower level of O_2 uptake during the first 10 minutes was thereby considered to be due to the further depletion of O_2 stores so that the apparent uptake was less than the actual. By subtracting the quantity of O_2 represented by the area enclosed by the apparent and actual steady-state O_2 uptake during the first 10 minutes of hypoxia from the total area described as the O_2 deficit, an independent estimate of the change in O_2 stores is then utilized to derive what has been called the "true" O_2 deficit. A comparison (fig. 6) between the two methods of finding "true" O_2 deficit, by calculation and by graphic means, yields a linear relationship with a high coefficient of correlation and a positive intercept on the ordinate of about 5 ml. kg. It is impossible to say whether there was a consistent overestimate of O_2 stores by calculation or an underestimate by the graphic method to account for the positive intercept. One fact is apparent, however. As the O_2 deficit gets larger, the change in O_2 stores becomes less important as a possible source of error. A larger scatter of points occurs below 20 ml. kg. of O_2 deficit; whereas above that, points lie closely along the line calculated by the method of least squares.

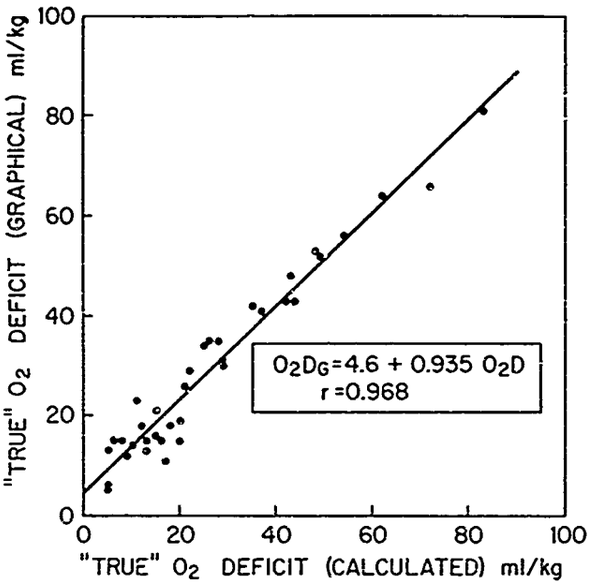

FIGURE 6

The "true" O_2 deficit obtained by subtraction of the calculated changes in O_2 stores (O_2D) from the total measured O_2 deficit is shown in relation to that obtained by estimating change in O_2 stores from the graph of oxygen uptake against time (O_2D_t).

The results from these experiments contribute no new knowledge about O_2 debt and its significance. They do, however, define more carefully the interrelationships of O_2 deficit, excess O_2 of recovery, and excess lactate which are present when concentration of oxygen is presumably the limiting link in the chain of oxidative metabolism.

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	USAF School of Aerospace Medicine Aerospace Medical Division (AFSC) Brooks Air Force Base, Texas

13. ABSTRACT

The oxygen deficit incurred during hypoxia was compared to the peak excess lactate (XL) level in order to see if any consistent relationship existed when a known oxygen limitation was imposed. Twelve anesthetized dogs, in which ventilation was held constant, breathed 9.1% O_2 in N_2 for 10, 20, and 30 minutes. Oxygen uptake was measured every 10 minutes during a control period, hypoxia, and a recovery period. Oxygen content and tension of systemic and pulmonary arterial blood were measured at the end of each of these periods. Excess lactate was calculated from blood lactate and pyruvate levels measured during the control period, the last minute of hypoxia, the first minute of recovery, and at intervals thereafter. Depletion and repletion of oxygen stores were estimated by assuming values on a body-weight basis for functional residual volume, body water, total blood volume, and its distribution. "True" O_2 deficit and "true" excess O_2 of recovery were thus calculated and compared to each other and to peak XL values. Excess O_2 uptake measured during recovery, which is the oxygen debt as usually measured, never was as great as the oxygen deficit incurred during hypoxia, and bore little consistent relationship to peak XL. The "true" O_2 deficit, on the other hand, had a coefficient of correlation of .781 when compared with peak XL.

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Physiology						
Oxygen debt						
Oxygen stores						
Hypoxia						
Lactate, excess						

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