RELATIONSHIPS OF PYRUVATE AND LACTATE DURING ANAEROBIC METABOLISM. II. EXERCISE AND FORMATION OF O_2-DEBT [1]

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On the basis of previous studies, it has been suggested that lactic acid production by tissues may be regarded as a function of the effectiveness of oxygen supply to them (1–3). However, these studies are subject to certain technical objections (4), and various other investigations have appeared to show either a different relationship (5, 6) or no relationship of lactate to O_2-debt (2, 7, 8) or hypoxia (9). Furthermore, a variety of conditions unrelated to oxygen deficiency have been found to cause lactate production in the intact body (4). Therefore, it seems unwarranted at present to ascribe alterations in body lactate, or in lactate exchanges of organs, to oxygen deficiency of the tissues.

The essential element of the original suggestion by Hill, Long, and Lupton that lactate production is associated with oxygen deficiency in the intact body was an apparent relationship between lactate and O_2-debt found under very special circumstances (1, 10, 11). We have been unable to confirm this relationship strictly, as will be seen in the present data. The development of knowledge about the lactic dehydrogenase system in recent years, moreover, makes such a relationship appear to have been a special circumstance rather than a general principle, since changes in pyruvate affect lactate levels as much as does oxygen lack (4), and the fundamentally parallel effect of pyruvate and hypoxia on lactate production is shown by the equation of the lactic dehydrogenase equilibrium. If a lactate change, however, exceeds that which is appropriate, according to this relationship, to the alterations in pyruvate, then there would appear to be only one explanation for the excess, *i.e.*, oxygen deficiency. Calculations of this "excess lactate" (XL) previously made (4) show this quantity to be essentially zero during marked lactate production from nonhypoxic causes. The present data on exercise indicate the magnitude of "excess lactate" production during tissue hypoxia and the quantitative relationships between total lactate, XL and respiratory O_2-debt.

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METHODS

Human subjects without cardiac or respiratory disease came to the laboratory fasting and rested for an hour or more in bed after an indwelling needle was placed in one brachial artery with local anesthesia. Exercise was carried out by two methods for the purpose of producing O_2-debts of various magnitudes. The severe exercise consisted of walking on a motor-driven treadmill; the mild exercise consisted of straight leg raising in the supine position. No further attempt was made to regulate the work done. Exercise lasted from 7 to 15 minutes.

Blood was collected from the brachial artery as previously described (12) at frequent intervals during rest, exercise and recovery. Recovery was followed for one and one-half to two hours. Samples were analyzed for lactate, pyruvate and oxygen as previously described (4). Blood oxygen saturations exceeded 96 per cent in every instance.

Expired air was collected continuously during the severe exertion and intermittently during the mild exercise; collection was continuous from the last minute of exercise throughout the recovery period in all experiments. Timed air collections were carried out through a rubber mouthpiece, low resistance valve and short length of tubing leading to two Douglas bags used alternately. The volume of gas in each bag was determined either by drawing the contents through a carefully calibrated wet-test gas meter at constant pressure and rate of flow, or by determining the dilution volume of a measured quantity of acetylene in the bag. The expired air was analyzed for oxygen and carbon dioxide either in the Haldane apparatus or in the paramagnetic oxygen analyzer (Beckman, Model E2 null-point analyzer with total range 12 to 22 per cent) before and after passage through soda-lime and sodium hydroxide. The analyzer was used at constant pressure and rate of flow. Collection periods were two to five minutes in length. From the volume and composition of inspired and expired air, rate of oxygen consumption was obtained for each period. Total body water was determined in each subject as the dilution volume of 4-aminoantipyrine (13).

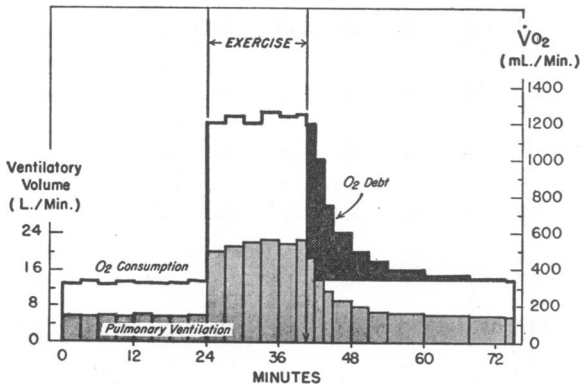

FIG. 1. TYPICAL CHANGES IN VENTILATORY VOLUME AND MINUTE UPTAKE OF OXYGEN BY THE LUNGS IN A SUBJECT DURING STANDING TREADMILL EXERCISE

Total O_2-debt (the shaded area) is calculated as the integral of the $\dot{V}_{O_2}$ curve between the moment exercise ceases and that at which the slope of the curve becomes zero. The measurement of the late portions of this area may be seen to be subject to considerable error since the rates of oxygen consumption are only slightly increased over the plateau rate.

The experimental dogs weighed 10 to 20 Kg. and were anesthetized with 20 mg. per Kg. of chloralose. Exercise was effected by rhythmic electrical stimulation through electrodes inserted into the tissues near the spine and tips of the feet. Collection and analysis of blood and gas samples were the same as for the human subjects except that each recorded blood concentration is the mean of determinations on blood collected simultaneously from the aorta through a femoral cannula and from the right ventricle through a large bore cannula inserted through the jugular vein.

RESULTS

Figure 1 shows a graph of typical oxygen consumption rates plotted for one human subject during an exercise procedure. The shaded area represents the O_2-debt contracted. The O_2-debt remaining at each time, t_n, during recovery is given by the integral of this curve between t_n and t_o, the latter being the time when oxygen consumption ceases to change. When these values are plotted, an "O_2-debt curve" is obtained;[2] this curve is the only one shown in subsequent figures.

Total body lactate was calculated from the concentration of lactate per liter of blood water, by multiplying by the volume of body water. This conversion involves the assumption that the added lactate during exercise has a virtual volume of dilution approximately equal to total body water, an assumption which will be discussed below. Total body lactate in millimoles is then multiplied by its oxygen-equivalence factor, 0.5 mM oxygen (11.2 ml.) per mM lactate. This permits O_2-debt and body lactate to be expressed in the same units for comparison. Neither multiplication, of course, alters the contour of the time curve.

[2] $O_2\text{-debt}_{t_n} = \int_{t_n}^{t_o} (\dot{V}_{O_2} - \dot{V}_{O_{2t_o}})\, dt.$

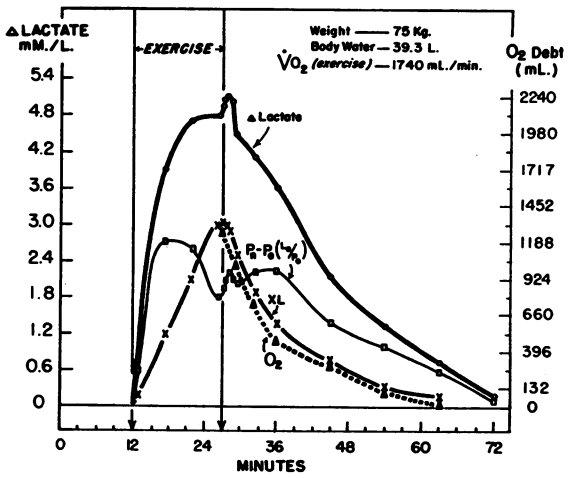

FIG. 2. O_2-DEBT CONTRACTED BY A SUBJECT DURING MODERATELY SEVERE EXERCISE, CALCULATED FROM ΔLACTATE (CHANGE IN BLOOD LACTATE OVER RESTING CONTROL VALUES), FROM EXCESS LACTATE (XL), AND FROM OXYGEN CONSUMPTION MEASUREMENTS (O_2)

Also plotted is the correction factor $P_n - P_o$ (L_o/P_o) (see text). All values are given both in millimolar equivalents of lactate and milliliter equivalents of O_2-debt.

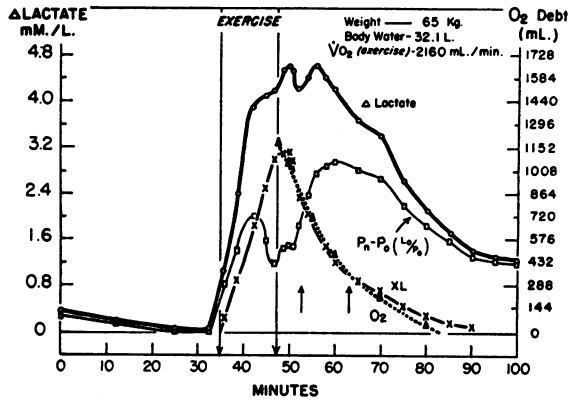

FIG. 3. EFFECT OF CHANGES IN PULMONARY VENTILATION ON THE FORM OF THE O_2-DEBT CURVES FOLLOWING MODERATELY SEVERE EXERCISE IN A HUMAN SUBJECT

The vertical arrows near the baseline indicate the time the subject was instructed to "breathe faster and deeper."

"Excess lactate" or XL is calculated as previously described (4) by the following equation:

$$1)\quad XL = (L_n - L_o) - (P_n - P_o)\ (L_o/P_o)$$

where L_n and P_n are lactate and pyruvate concentrations at any time t_n; L_o and P_o are the levels obtained as a plateau of three or more samples in the near-basal state. The variance of XL, as judged from multiple blood samplings in succession from patients in a near basal state, is ± 0.01 mM per L., or about 5 ml. oxygen, for confidence limits of 95 per cent.

Figures 2 to 5 show plots of $(L_n - L_o)$ (converted to O_2-debt equivalents as described) and also of the second term of equation *1*), $(P_n - P_o)$ (L_o/P_o), similarly converted to oxygen-equivalents. The shape of the latter curve depicts the relative changes in pyruvate observed in the experiment, and its height indicates the quantity of lactate present solely as a result of alteration in pyruvate. The remainder of lactate in excess of this, the presence of which is ascribable to the only other factor affecting lactate production, oxygen lack, is plotted as XL (converted to oxygen-equivalents as described for total lactate).

It can be seen from the figures that total lactate varies with time in a manner wholly different from O_2-debt. Similar observations have been made by Jervell (2). The oxygen equivalents of lactate usually far exceeded the O_2-debt, although occasionally they were much less. The absolute values in these figures might be changed by using a different volume of distribution of lactate, but no single value could reconcile the irregular time curves of lactate with those of O_2-debt. Figure 2 shows the smooth falling curve of blood lactate which may be observed in a calm subject, who is thoroughly accustomed to the procedures and whose pulmonary ventilation falls off during recovery in a similar, almost exponential, fashion. This is the type of result seen in trained subjects. Figure 3, however, shows the effect of irregular ventilation during recovery; the lactate curve is no longer smooth. Regularity of lactate curves, when present, is a characteristic probably due to the coincidence of a regularity of ventilation during recovery, and one which we have rarely observed in patients. Pulmonary ventilation with respect to carbon dioxide is known to have a marked effect on lactate production (4).

Figure 4 shows an exercise period in an athletic young man in good physical training, and illustrates a downward error in the lactate estimation of O_2-debt. Such negative lactate errors always occurred in association with decrease of pyruvate, a phenomenon which appears to occur much more commonly in subjects in athletic training, as has been suggested previously (14).

Figure 5 shows the changes in a subject during very mild exercise. Mild exercise has been be-

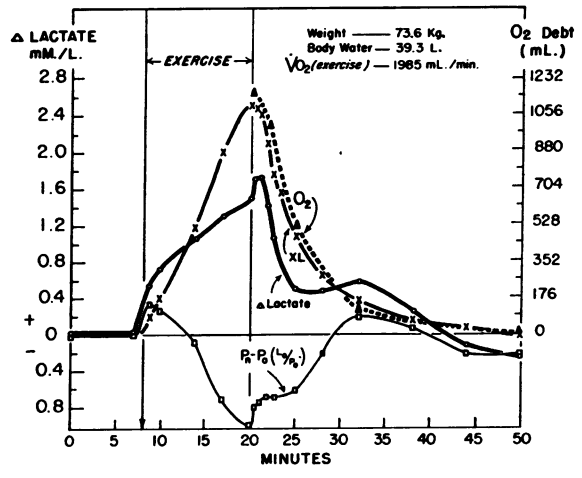

FIG. 4. THE EFFECT ON O_2-DEBT CURVES OF A FALL IN BLOOD PYRUVATE

This phenomenon was occasionally observed during exercise and occurred in athletic young men in physical training; only when pyruvate fell was the lactate curve lower than the true O_2-debt curve.

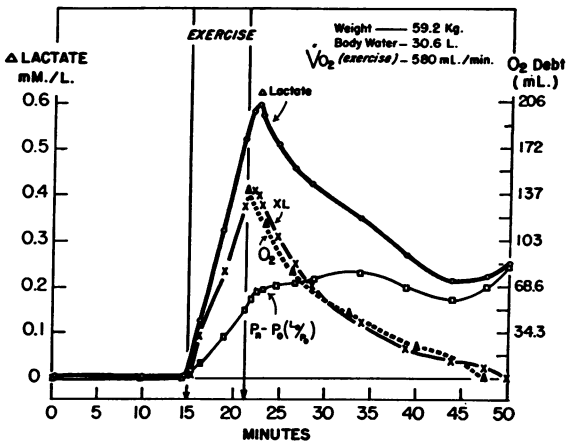

FIG. 5. O_2-DEBT CURVES OF A SUBJECT DOING VERY *MILD* EXERCISE IN THE SUPINE POSITION

Oxygen consumption was increased only 2.5-fold, but the curves after exercise stopped are essentially the same as in severe exercise.

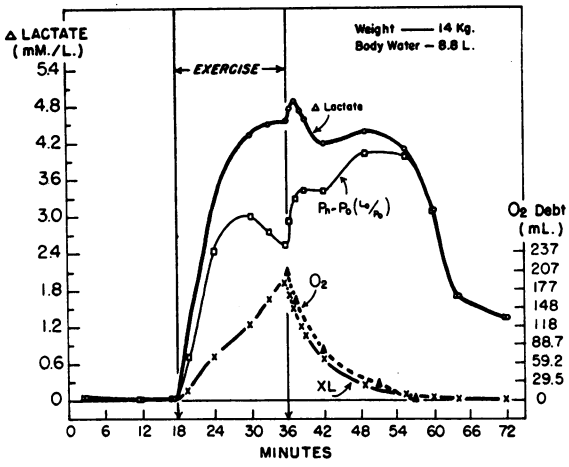

FIG. 6. EFFECT OF ELECTRICALLY INDUCED EXERCISE OF THE ENTIRE BODY IN AN ANESTHETIZED DOG (V_{O_2} INCREASED 6-FOLD) SHOWING EXTREME DIVERGENCE OF THE TIME CURVE OF BLOOD LACTATE FROM THAT OF O_2-DEBT

Close correspondence of XL and O_2-debt is seen in spite of the great difference of body weight and proportion of body water from those in the previous figures.

lieved to be fundamentally different from harder exercise (1, 8). The curves, however, appear to be identical with those of severe exertion except in height on the ordinate, but the respiratory O_2-debt, of course, approaches values which are unmeasurable by available techniques, and this may account for the belief in the older literature that mild exercise either produces no oxygen debt (8) or one with a different decay curve (1). Since no basic difference in anaerobic metabolism of tissues is apparent at any grade of exercise, it now seems quite possible that the changes are the same even during exercise too mild to produce a detectable or measurable respiratory oxygen debt. This is suggested also by the fact that excess lactate production is apparent in all subjects after the first two or three muscle contractions of mild supine exercise (within the first minute), as shown in the illustrations.

In all the figures the O_2-debt curves pursue the regular course long found to be characteristic (1, 9). It is notable that the curves of excess lactate are quite similar to those of O_2-debt both in height at any one moment and in contour, and are often nearly superimposable. This is true not only in Figure 2, when the lactate curve is smooth, but also in experiments like that of Figure 3 when total lactate is variable. XL approximates O_2-debt whether total lactate is too high (Figures 2, 3, and 5) or too low (Figure 4). Thus, whether lactate will be found to be excessively high or too low, appears to depend a great deal on how much, and in what manner, pyruvate changes [*i.e.*, curve $(P_n - P_o)$ (L_o/P_o)].

These same phenomena are illustrated in Figure 6 showing the effects of electrically induced muscular exercise in an anesthetized dog. These experiments extend the observations to include recovery from exercise under complete anesthesia, free of psychic influences and slight muscle movements unavoidable in patients, and extend the range of body size studied down to 10 Kg. weight. Figure 7 illustrates the effect of altering the pump-controlled respiration ($\dot{V}$) of a dog during an exercise period and more clearly emphasizes the complete independence of lactate from O_2-debt. Frequently, arterial blood lactate in unanesthetized human subjects begins to rise prior to the actual beginning of muscle movements, in anticipation of the order to exercise. This phenomenon was not seen in anesthetized dogs.

The sharp peak in lactate curves shown in the figures at the onset of rest was present in all experiments. The highest value for blood lactate was always reached within 90 seconds (average 50 seconds) after the cessation of exercise. There was commonly a similar rise in pyruvate concentration so that XL actually was maximal at the in-

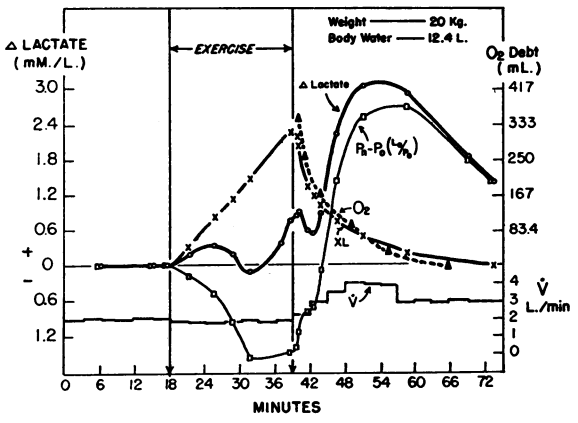

FIG. 7. EFFECTS OF ARBITRARILY ALTERING THE PUMP-CONTROLLED RESPIRATION ($\dot{V}$) OF AN ANESTHETIZED DOG DURING ELECTRICALLY INDUCED MUSCULAR EXERTION, SHOWING THE COMPLETE INDEPENDENCE OF BLOOD LACTATE AND O_2-DEBT

stant of cessation of exercise and fell during the first minute. The maximum rise in pyruvate was much later and varied in time between 7 and 22 minutes (average 12 minutes) after the beginning of rest; (Figure 4 shows an unusual late peak occurring at 35 minutes). This timing of the pyruvate peak is the same as that seen in hyperventilation (8); it is not an inherent characteristic of the rate of uptake of pyruvate by body tissues, however, since the level drops sharply after infusions of pyruvic acid. These same characteristics of the time curve are likewise seen in respiratory hypoxia (15).

In all, 12 "severe" exercise experiments were carried out on five male subjects and one female. Table I shows the body weights, body water contents, rates of oxygen consumption at the end of exercise, and total respiratory O_2-debts. Similar figures are given for the 11 instances of supine (mild) exercise in nine subjects. The errors of estimating O_2-debt from lactate and XL are not adequately represented in the first blood sample

TABLE I

Total O_2-debts calculated from total blood lactate change (ΔL), "excess lactate" (XL), and analysis of respiratory gas (column marked "O_2-debt") in human subjects

Subject	Wt. *Kg.*	Body water *L.*	$\dot{V}_{O_2}$* Exer. *ml./min.*	$\dot{V}_{O_2}$* %Δ	Time *min.*	O_2-debt From $\dot{V}_{O_2}$ *ml.*	O_2-debt From ΔL *mM/L.*	O_2-debt From ΔL O_2 equiv. *ml.*	O_2-debt From XL *mM/L.*	O_2-debt From XL O_2 equiv. *ml.*
Upright exercise (strenuous)										
Ia	75	39.3	2,960	842	20	3,170	4.750	2,090	7.040	3,098
b			1,740	454	15	1,280	5.091	2,240	3.005	1,320
c			995	217	10	410	1.902	837	0.920	405
IIa	82.8	42.4	3,577	971	20	4,550	11.880	5,640	9.538	4,525
b			2,008	498	20	2,300	9.168	4,350	4.613	2,190
c			1,240	271	15	978	4.369	2,072	2.043	970
IIIa	86.8	42.5	1,990	501	15	1,420	6.810	3,240	3.159	1,504
b			2,457	642	15	2,260	3.109	1,480	4.938	2,150
IVa	62.3	29.6	2,985	1,230	15	1,650	5.249	1,740	4.855	1,610
			2,290	842	15	1,830	6.681	2,215	5.601	1,858
V	65.0	32.1	2,160	586	12	1,160	4.619	1,660	3.170	1,140
VI	73.6	39.3	1,985	266	14	1,140	1.702	749	2.491	1,096
Supine exercise (mild)										
I	72.7	36.5	888	205	10	298	1.542	630	0.743	304
II	56.8	27.6	774	250	12	464	0.964	298	1.392	430
III	81.8	43.0	1,007	198	7	222	0.914	440	0.509	245
IV	64.6	34.4	587	110	9	144†	0.649	250	0.364	140
V	77.8	40.3	584	80.2	10	104†	0.554	250	0.217	98
VI	54.5	27.0	880	300	11	385	1.349	408	1.250	378
VIIa	74.6	37.8	489	60.8	9	82†	0.595	252	0.201	85
b			1,205	297	12	508	0.718	304	1.226	519
VIIIa	91.8	43.6	980	187	10	346	0.776	379	0.696	340
b			582	70.2	11	159†	0.578	282	0.297	145
IX	59.2	30.6	580	152	8	140	0.612	210	0.404	138

* $\dot{V}_{O_2}$ = Rate of oxygen consumption.
† See footnote 3.

after exercise, but often showed greater or lesser divergence at other moments of recovery. For this reason a statistical comparison was made between the values by all three methods (respiratory, blood total lactate and blood XL) at each moment when all three were available. In this sense, 150 O_2-debts were estimated by three methods. The "errors" [3] of total lactate as an estimate of O_2-debt averaged 982.5 ml. oxygen ($\sigma = 743.5$) or 119.5 per cent ($\sigma = 90.4$ per cent). The errors of XL averaged -41.3 ml. oxygen ($\sigma = 89.6$) or -5.0 per cent ($\sigma = 10.9$ per cent). The difference between the two means is highly significant, ($p < 0.001$).

Eighty-seven O_2-debts were estimated by three methods in six dogs. The errors of total lactate as an estimate of respiratory O_2-debt averaged 308 ml. oxygen ($\sigma = 188.9$) or 153.2 per cent ($\sigma = 94.0$ per cent). The errors of XL averaged -12.5 ml. oxygen ($\sigma = 16.9$) or -6.2 per cent ($\sigma = 8.4$ per cent). Again the difference was highly significant. The errors in estimating O_2-debt by either method in human subjects and anesthetized dogs were both positive and negative, but a tendency to large positive errors was common for total lactate, while a mean tendency to slight underestimation is evident for XL. This small "negative error" for XL may possibly represent the extent of "positive error" in respiratory O_2-debt measurement due to resaturation of the oxygen pool of the body, a problem which is discussed more fully in the following paper (13), but one which probably is also a feature of exercise experiments (16) to a lesser extent.

DISCUSSION

From previous studies it is clear that lactate production is not controlled by a single factor but by the two factors on the right of equation *2*) in the first paper of this series (4). Lactate changes could be expected to reflect alterations in the oxygen-supply factor only if pyruvate remained constant. If pyruvate changes at the same time as $[DPNH_2]/[DPN]$, the total lactate change will not accurately measure either factor alone. In other words, the system may be subjected to a change in both pyruvate and lactate concentrations simultaneously without any alteration in its balance; this occurs during alkalosis, the infusion of glucose or pyruvate and the administration of insulin or epinephrine (4). On the other hand, the system may also be found to shift its balance to the right, as it does in hypoxia. In actual experience, both changes occur in exercise. The present data give no indication of the basic reason for the alterations in body pyruvate; the control of pyruvate levels in the intact body is too complex to warrant speculation as to their immediate cause at this time. The control of lactate concentrations, however, is far simpler, since lactate takes part in no other equilibrium than that of the lactic dehydrogenase system.

The results obtained in the present experiments depend to some extent upon the methods of blood collection and analysis. If venous blood is sampled from an arm vein during exercise of the legs the concentrations of lactate, pyruvate and XL are significantly lower than those in the mixed venous blood which drains the entire body. The changes shown in the illustrations occur in arterial and mixed venous blood almost immediately on the first movement of exercise (within 30 to 60 seconds) and they continue throughout any period of exertion of this duration. We have found that little or no change occurs in blood draining the resting muscles of the arm, however, for some minutes, if at all. This effect of resting tissues on blood levels may well explain the failure of earlier workers (2, 8, 17–19) who sampled only venous blood, to find any change in blood lactate except in severe exercise. It seems likely that this is also the explanation for some of the anomalously low blood lactate values reported during exercise (5), although the low values which appear to be characteristic of athletes also are an important part of previous studies (8, 19).

Differences in concentration in various parts of the body make the idea of a gross anatomical volume of perfectly uniform distribution of lactate and

[3] The differences from the respiratory O_2-debt values are here referred to as errors, but these differences also include the "error" or variability of the respiratory measurement itself. This technical error may be quite large for small values of O_2-debt. When comparisons are omitted from the statistical calculations for all periods when the elevation of oxygen consumption over basal was less than 10 per cent, however, the mean figures are not significantly different from those given. The small O_2-debts in Table I marked with a dagger were determined with 20 second to 1 minute sampling of expired air in Douglas bags in which both the dead space volume of pure nitrogen and the final volumes were determined by dilution of measured quantities of acetylene, and analyses were all done in the Haldane apparatus.

pyruvate inaccurate, of course, since the distribution is not actually uniform. The present data, however, suggest that the factor relating the concentration of XL in blood water to total body XL is, in fact, approximately equal to the body water content for a great variety of body sizes and grades of exercise. The concept of a virtual volume of distribution is, therefore, useful here.

On the other hand, aside from the mere usefulness of the concept, blood lactate changes have been shown actually to reflect those of tissues accurately (20), and the apparent volume of distribution of lactate in living muscle has been found to be that of the total tissue water content (21). There is evidence that lactate and pyruvate cross certain cell membranes passively (12), and in intact man and dogs, rapidly enough (4) to permit blood determinations by the present methods to depict intracellular events with sufficient reliability if changes are no more sudden than these. However, the application of such a principle to the study of sudden, brief bursts of maximal exercise might be unwarranted.

The present data for recovery periods after exercise indicate that an O_2-debt may be paid off completely while body lactate is still elevated above basal levels or even rising further, *i.e.,* that all the accumulated lactate need not be oxidized when the O_2-debt has disappeared, but only that it bear a certain relationship to body pyruvate so that metabolic oxidations have returned to normal rates. Whether pyruvate is increased or decreased has no apparent effect on O_2-debt. Thus, oxidation of lactate to pyruvate is the step responsible for the consumption of oxygen, and the subsequent fate of the pyruvate seems not to be involved. This is easy to understand in terms of the total rate of flux of the pyruvate pool, which is very large by comparison with the tiny rate of formation from lactate during recovery from exercise (the latter might be equivalent to 15 to 20 ml. of oxygen per minute while the former would be equivalent to 1,000 ml. of oxygen per minute). If this small rate of appearance of pyruvate within cells inhibited pyruvate synthesis from carbohydrate alone, for example, by only 1 to 2 per cent, it would affect neither the pyruvate concentration of the body nor the rate of consumption of oxygen. Thus the O_2-debt equivalent of excess lactate can be assigned a theoretical value of 0.50 mM oxygen per mM XL, the quantity required for conversion to pyruvate. This 11.2 ml. of oxygen per mM XL (1 ml. of oxygen for 8.03 mg. of lactic acid) is remarkably similar to the empirically chosen value of 1 ml. for 7 mg. of lactic acid used by earlier workers (1) for lack of a theoretical value. Use of the latter factor in the present calculations, instead of the theoretical value, would only have increased the already large divergence of lactate from O_2-debt.

While the present data support the idea that lactate production by tissues has no necessary significance with respect to oxygen supply, they suggest that a function of both lactate and pyruvate may, on the contrary, have such significance. The unique information provided by O_2-debt measurement in those very special types of experiments in which the measurement can be made has been appreciated for many years. The phenomenon of O_2-debt formation appears to be a manifestation of a need for oxygen by body tissues during exercise, a need which is not met at the time but satisfied only later during recovery. This unique evidence of oxygen lack appears when blood oxygen content and tension are normal and the rate of delivery of oxygen to the tissues per minute is greater than normal. The metabolic basis of this "energy-borrowing" has, however, remained obscure in spite of attempts to relate it to lactate accumulation. The calculations presented here help to explain the relationship between O_2-debt and tissue anaerobic metabolism; they suggest that the relationship is only slightly more complex than proposed by Hill, Long, and Lupton (1). The error which may occur from using lactate production *per se* as an indication of tissue oxygen lack, however, is very variable and sometimes large. The use of "excess lactate" for this purpose should reduce the error significantly.

It has been suggested that the ratio of lactate to pyruvate actually tends to remain constant at various levels of exertion differing greatly in severity (22, 23), a suggestion which is obviously denied by the present data. This suggestion, however, was derived from extremely variable figures from the point of view of the present computations ($\pm$ 1.0 mM per L. lactate, $\pm$ 0.07 mM per L. pyruvate, and lactate-pyruvate ratios varying by as much as 20). The variability in these reports exceeds the total changes occurring in many of the present experiments. Such variations in the simple ratio, of course, might have negligible

quantitative significance as was assumed in the previous work, or very great significance in any individual case, as pointed out in the first paper of this series (4). Calculated excess lactate, for instance, would be much greater for any given change of lactate-pyruvate ratio in the high range of P_n than at low pyruvate levels. In any event, the present experiments deal with the meaning to be assigned to alterations well within the magnitude regarded as random variance in the studies cited.

At the onset of exercise the rate of oxygen consumption rises to a new level where it remains as long as the rate of exertion is constant. The new V_{O_2}, however, is not achieved instantly but only after one to three minutes of exercise, and the energy expended in performing the exercise during this brief period is sometimes referred to as the "oxygen deficit." In severe or prolonged exercise the "oxygen deficit" is quite small relative to the O_2-debt, but it is more important in lesser exercise. Since the curves of XL accumulation do not indicate that the "oxygen deficit" is supplied entirely by the mechanism which has been the subject of these investigations, it appears that some other source of energy is used if the effort can be assumed to be constant from the first moment of exercise. Actually, the effort may well be less in this first minute than subsequently, but there appears to be no way of determining this with certainty. There is a net diminution of oxygen stored in hemoglobin in the body, and this oxygen presumably supplies a portion of the early energy requirement. In the mild exercise studied the mean change in mixed venous blood oxygen content was 30 ml. per L. in the first two minutes, thus providing about 100 ml. of oxygen during this period in the human subjects. In addition, the slope of the XL curve is greater in the first minute of exercise than subsequently, although this difference is not readily apparent in the illustrations. Finally, evidence from other types of experiment suggest that a net reduction of high energy phosphate compounds in tissues may supply another portion of the oxygen deficit (24), although in the present experiments this has appeared to be small in the mild exercise, after the measurable factors above have been taken into account. The oxygen supplied from hemoglobin and myoglobin is restored during the first minute of resting recovery from exercise and constitutes an "error" in the measurement of O_2-debt as a metabolic phenomenon. The remaining or corrected O_2-debt is found to be slightly more than the quantity of energy made available from the LDH system and this difference may represent the extent to which initial diminutions of the myoglobin oxygen and high energy phosphate pools have failed to be restored before the onset of rest at the end of exercise.

SUMMARY AND CONCLUSIONS

1. Changes in blood lactate in exercise are not correlated with excess oxygen consumption of recovery (O_2-debt) in human subjects or anesthetized dogs, and may err in either direction.

2. Calculated "excess lactate," a function of changes in both pyruvate and lactate, is well correlated with O_2-debt, regardless of the direction or magnitude of the lactate error, erring by an average of -5 per cent ± 11 per cent.

3. The metabolic alterations which are responsible for oxygen debt formation in exercise are essentially similar at all grades of exertion, great and small, and are probably also the same in exertion too slight to produce an oxygen debt which is detectable by available respiratory methods.

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