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Anaerobic Capacity: Past, Present, and Prospective

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Lars Hermansen had many research interests, but none was more important to him than the glycolytic energy release during exercise and the effects on muscle pH, and how this influences fatigue as well as the recovery from exercise. In evolution, the anaerobic capacity has been an essential component for survival, maybe more so for our ancestors as hunters than a high aerobic capacity. A remnant of this may be the extremely high potential for glycolysis that still persists in skeletal muscle of humans. This is shown by the high glycolytic enzyme levels, which need only to be minimally activated for a very pronounced ATP production to occur by glycolysis. Glycogen can also be stored in all skeletal muscle fiber types of humans to an extent that is above that found in most other species.

Today a high maximal anaerobic capacity has no practical significance other than in certain sport disciplines. What should be remembered, however, is the paramount role anaerobic energy release has in allowing for very quick alterations in muscle power output, which thereby does not depend on the gradual increase in aerobic ATP production. This presentation starts with an overview (past), followed by presenting some results from ongoing experiments at our institute (present). In closing, critical unsolved issues are identified and research strategies are discussed, as well as sites for possible adaptation (prospective).

Past

Oxygen Deficit (Debt) and Its Utilization

In 1919/1920 Krogh and Lindhard published a paper in the *Journal of Physiology* on "The Respiration at the Transition From Rest to Work" (48). The lag of oxygen uptake was quantified and defined as oxygen deficit (Figure 1). They also followed the oxygen uptake in recovery and made the observation that at light exercise intensities, the recovery oxygen uptake above basal (resting) metabolic rates (oxygen debt) matched the oxygen deficit, whereas more intense or exhaustive exercise led to larger debt than deficit (Figure 2). The reason was that recovery oxygen uptake was slow in returning to preexercise level. Indeed, it may not have returned to resting levels the same day as the exercise!

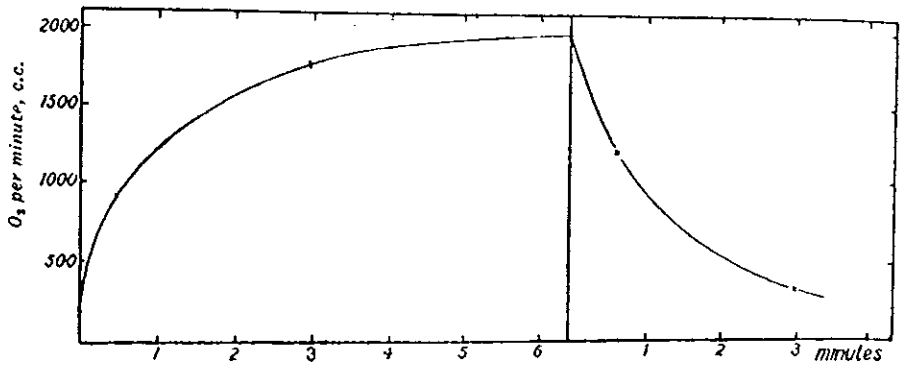

Figure 1. Original figure (No. 4) from the paper by Krogh and Linhard (48), where they measured the oxygen uptake in transition from rest to exercise and in recovery. The oxygen uptake after 5-6 min of exercise represents the energy demand at this intensity because the work was submaximal.

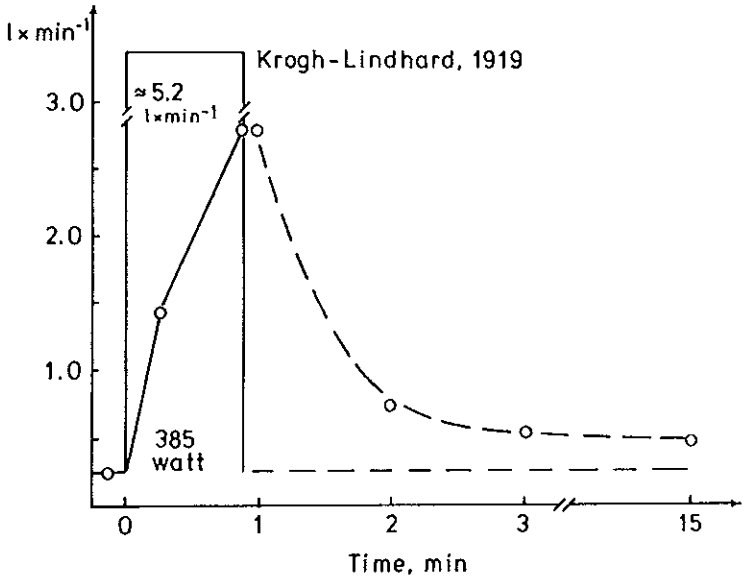

Figure 2. These data from Krogh and Linhard's publication (48) illustrate their results of very intense work performed to exhaustion. The same subject repeated the exercise at some interval (different days) to achieve complete measures of the oxygen uptake during the quite short exercise period (~ 50 s).

Long before measurements of oxygen deficit and debt were performed, lactic acid had been determined in blood and muscle and was associated with a lack or a limited supply of oxygen (3, 4, 49). Before these reports lactic acid had already been linked

with intense physical exertion because a high level of lactic acid had been found in exhausted game (see 8). The literature an anaerobic energy metabolism flourished early in this century (for references, see 38) and culminated after Lundsgaard (54, 55) had demonstrated that muscle unable to produce lactic acid, due to iodoacetate poisoning, could still contract. This paved the way for understanding that CP and ATP are the energy-rich compounds that are the more immediate energy sources for muscle contraction (52, 53). Detailed studies followed on factors of importance for lactic acid formation in exercising humans (7, 65); how the lactacid and alactacid (ATP/CP) anaerobic energy yield contributed to the oxygen deficit (56); and how the repayment of the oxygen debt, as defined by Krogh and Linhard (48) and Meyerhof (61), occurred (13, 16, 45, 58). In essence, they could demonstrate a first, very fast component of repayment lasting some minutes and a second, quite slow component. Resynthesis of ATP and CP as well as reloading of hemoglobin and myoglobin were linked with the first phase, the metabolism of lactate with the second phase, although lactate clearance was not the only cause.

Early studies by A.V. Hill are also available on the utilization of the oxygen deficit in exercise. He found that an even pace was most economical in a race (31, 32). This concept has been challenged by Secher (79), who argues that in racing over a fixed distance, the intensity (speed) should be the highest at the onset of the exercise. This produces the fastest rate of acceleration of the oxygen uptake. A point that has support is the fact that the rate of rise in oxygen uptake at onset of exercise is a function of the relative exercise intensity (5, 50).

It is noteworthy that an oxygen deficit is a capacity; it is not a rate like maximal oxygen uptake, but it is utilized at a certain rate that may vary (see also Figures 1 and 2). The unloading of oxygen from hemoglobin and myoglobin is rapid, and the new, lower equilibrium concentrations for ATP and CP in the contracting muscles is also reached within 15-20 s (21, 40). The rate of the lactate production can be extremely high; 1-2 mmoles • kg^{-1} can be accumulated in the muscle over a few seconds (Figure 3), which demonstrates that, in contrast to earlier beliefs, an acceleration of the glycolysis starts at onset of dynamic exercise (35, 76). With this in mind, it could be anticipated that the entire oxygen deficit is utilized within 1 min or less. Data demonstrating complete usage in 1 min are available (39, 60). However, according to Medbø et al. (59), only 75% of the total oxygen deficit is utilized after 1 min of exercise, but after 2 min the whole capacity is exhausted. Special training may be critical and may be part of the explanation for differences in results.

Components of the Oxygen Deficit

The energy derived to cover the oxygen deficit is derived from glycolysis and also ATP and CP stores. At the start of the exercise, muscle ATP and CP concentrations are high ($\geq$ 30 mmoles • kg^{-1}); at exhaustion they are reduced up to 20% and 80-90%, respectively (47). Depending on the muscle mass involved in the exercise, the actual amount of this alactacid component of the oxygen deficit varies slightly. Moreover, aerobic processes are also included in a measure of the oxygen deficit because the oxygen bound to hemoglobin and myoglobin is reduced from the start to the end of an exercise period (12). The magnitude of these components

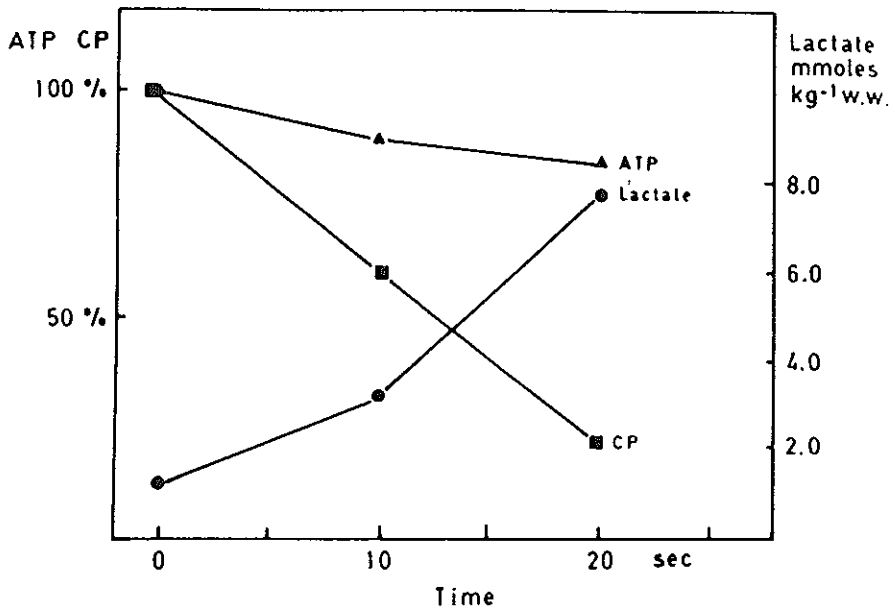

Figure 3. The reduction of ATP and CP and the increase in lactate of contracting muscles are depicted after onset of exercise (76).

is smaller than the lactacid components, and at maximum they amount to 30-40% of the total oxygen deficit (Table 1).

More important is that training produces only minor alterations in the absolute values for the contributions of these variables to the oxygen deficit. ATP and CP concentrations in muscle are basically unaffected by any type of training (see 75), and the degree of depletion during exercise is more a function of the relative intensity than the training status (47). Endurance training increases the amount of hemoglobin (and myoglobin?) and thus the oxygen stored, but again the magnitude of this factor is small compared to the total oxygen deficit. Thus, an elevation in the maximal oxygen deficit is a function of greater lactate production.

How to Measure Anaerobic Work Capacity

An accepted method to measure a person's anaerobic capacity is not yet available. Several routes have been tried, but objections on theoretical grounds can be made against the various trials to quantify the anaerobic energy yield. Measurement of lactate in blood after exhaustive exercise has frequently been used, and Margaria and associates (57) have gone the furthest to use such a measure to estimate the anaerobic energy release (see also 34). There are, however, several difficulties with this method. One is in identifying when an equilibrium between muscle and blood lactate concentration exists. Other problems are the variability of dilution space for lactate and of lactate's turnover rate (25, 29). Before an equilibrium is reached between muscle and blood, the lactate evenly distributed in the various water spaces

Table 1 Components of the Oxygen Deficit

Components	O_2 equivalents ($ml \cdot kg^{-1}$)		Percentage of total (%)	
	S[a]	AT[b]	S[a]	AT[b]
Oxygen stored to Hb and Mb	5	6	10	8
ATP and CP ("alactacid")	15	16	30	22
Glycolysis ("lactacid")	30	48	60	70
Total ml-O_2 Eq $-kg^{-1}$	50	70	100	100

Note. The exercise involves primarily the leg muscles (running or bicycling) (refs. 12, 21, 40, 47).

[a]Sedentary subjects. [b]Anaerobically trained subjects.

of the body, a large fraction of the lactate has been metabolized. Thus, although everybody would agree that lactate in the blood is an indication of glycolysis, it is equally true that it cannot give a reasonable estimate of the anaerobic energy yield. Thus, it is not a quantitative measure of anaerobic capacity.

It was mentioned above that the oxygen deficit accumulated during exercise was repaid during recovery. A measure of the recovery oxygen uptake beyond preexercise or resting value (oxygen debt) has also been proposed and used as a measure of the anaerobic capacity after intense exhaustive exercise. The procedure has been used by, among others, Lars Hermansen in collaboration with Jan Karlsson (see 39). Several drawbacks with this method limit its value. More energy is needed to use lactate as substrate for the synthesis of glucose (glycogen) than is liberated when lactate is produced. Further, an unknown quantity of lactate is oxidized, which will then not appear as "extra" oxygen consumption. The largest problem is related to the fact that factors other than elevated lactate increase the oxygen consumption of the body (see 46). When oxygen uptake measurements in recovery are used to estimate anaerobic capacity, a factor (2 or more?) has been used to convert the oxygen debt into an anaerobic energy yield. This can hardly be a recommended procedure. The third route is to determine the oxygen deficit as was done in the "old days." In short-term submaximal exercise, the use of the oxygen deficit has been used extensively as a measure of the anaerobic energy release, which may be reasonable (40; see also Figure 1).

Problems arise with exhaustive exercise. If this work exhausts the subjects within a short time, we can assume that a maximal value for the oxygen deficit is reached. However, the energy cost of the exercise must be accurately known to calculate the oxygen deficit. This is not difficult at submaximal work loads, where the steady

state oxygen uptake represents the energy costs. With exhaustive exercise, however, the validity of the estimate of the true energy cost is less certain. This uncertainty relates to both methods used to estimate the energy costs, which either assume a given mechanism efficiency or extrapolate from the submaximal relationship between work intensity and oxygen uptake. Such estimations are likely to underestimate the true energy expenditure during maximal work because mechanical efficiency may be lower in exhaustive than in submaximal exercise (73, 74). How much lower is unknown. In spite of some theoretical objections to using the maximal oxygen deficit (or accumulated oxygen deficit, as it is referred to by Medbø et al. [59]) as a measure of anaerobic capacity, it is the only method with the potential of being quantitative.

The most commonly used test to determine anaerobic capacity is probably the Wingate test. It has limited value. The work time is usually too short to exhaust the whole oxygen deficit. The shorter the work time, the more it is a measure of the components of oxygen deficit other than the contribution of glycolysis (see above and 9, 11). Further contractile factors and muscle strength may be more limiting than the energy delivery systems. Another limitation is that the test is performed on a bicycle. The basic limitation of a person's anaerobic work capacity is located in the contracting muscle (cells). Thus, a measure of the maximal anaerobic power is a reflection of the capacity of the specific muscles engaged in the test. Exercising on a bicycle is ideal for the cyclist, but it has less practical value for athletes in other sports.

Magnitude of the Anaerobic Capacity (Maximal or "Accumulated" Oxygen Deficit)

Although the concept of oxygen deficit is old, it has not systematically been used to evaluate the range of anaerobic capacities of humans. It appears that the magnitude of the maximal oxygen deficit is a reproducible measurement. With time to exhaustion ranging from 2-17 min, the same peak values are observed (Figure 4). Further, acute changes in the barometric pressure does not affect the maximal oxygen deficit (Figure 4).

Some data on maximal oxygen deficit from the Scandinavian literature are summarized in Table 2. The subjects studied had anaerobic capacities of around 40-70 ml "O_2 eq" • kg^{-1}. The low and middle part of the range is rather well established. The high end contains only a few observations, and only a few subjects were national-class competitors. More important, the athletes were not in "peak" training at the time for the study. A value of close to 100 ml "O_2 eq" • kg^{-1} or more may be a likely estimate for a good miler or pursuit cyclist.

Young prepubescent children appear to have a much lower anaerobic capacity than adults, as judged by Eriksson et al.'s data (20). These 11- to 12-year-old boys had anaerobic capacities of only 35 ml "O_2 eq" • kg^{-1}, and endurance-type training had only a very minor influence on such capacity. Both muscle and blood lactate concentrations were also low in these boys. Based on these findings, it has frequently been concluded that anaerobic events are unsuitable for young kids. However, that is not a proper interpretation; it only means that they perform less well in sprint-type events. However, they probably have the advantage of recovering quickly

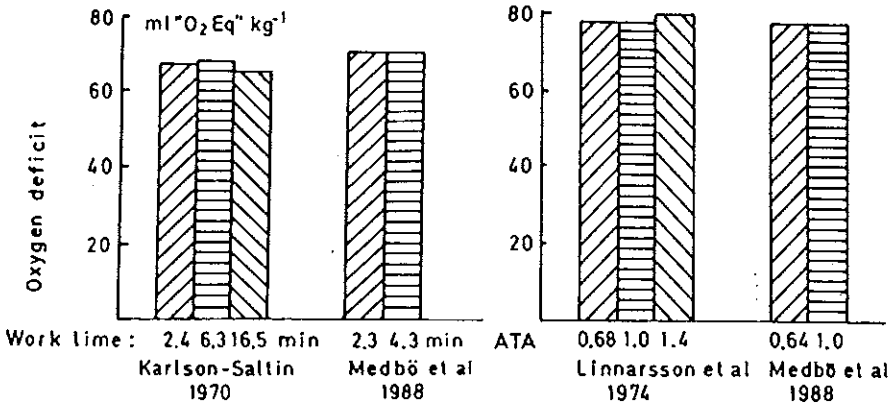

Figure 4. Summary of data in the literature on the maximal oxygen deficit in exhaustive exercise of different durations (left) and at different ambient pressures (right).

Table 2 Summary of Some Data in the Literature on Oxygen Deficit and Related Variables in Males

Reference	*n*	Age (years)	Training (status/test[a])	Weight (kg)	Oxygen deficit (L)	Work time (min)	Peak blood lactate (mM)
20	8	11.5	SED/B	44.7	1.48	~ 5	4.7
20	8	12.1	ET/B	45.4	1.64	~ 5	5.9
5	4	29	ET/B	77	6.25	~ 3	14.8
40	3	26	ET/B	74	4.95	~ 2.4	13.4
51	6	29	ET/B	75	5.75	~ 4	15.6
27	6	25	ET/R	70	3.15	~ 0.9	12.6
27	6	25	ST/R	75	4.06	~ 0.95	17.0
59	4	22	SED/R	74	4.72	~ 2	16.6
59	7	26	ST+ET/R	78	6.04	~ 2	16.6

Training status: sedentary, SED; endurance trained, ET; sprint trained, ST. Type of exercise used in the test: bicycling, B; running, R.

because less lactate has to be removed. After puberty, adolescent children have glycolytic enzyme activities similar to adults, and they then also exhibit "normal" blood lactate concentrations after exhaustive work.

Of importance is the fact that when more than the leg muscles are intensely involved in the exercise, as in whole-body exercise, the maximal oxygen deficit is much larger (Figure 5). This could be anticipated because the magnitude of the maximal oxygen deficit must be a function of the muscle mass engaged in the exercise.

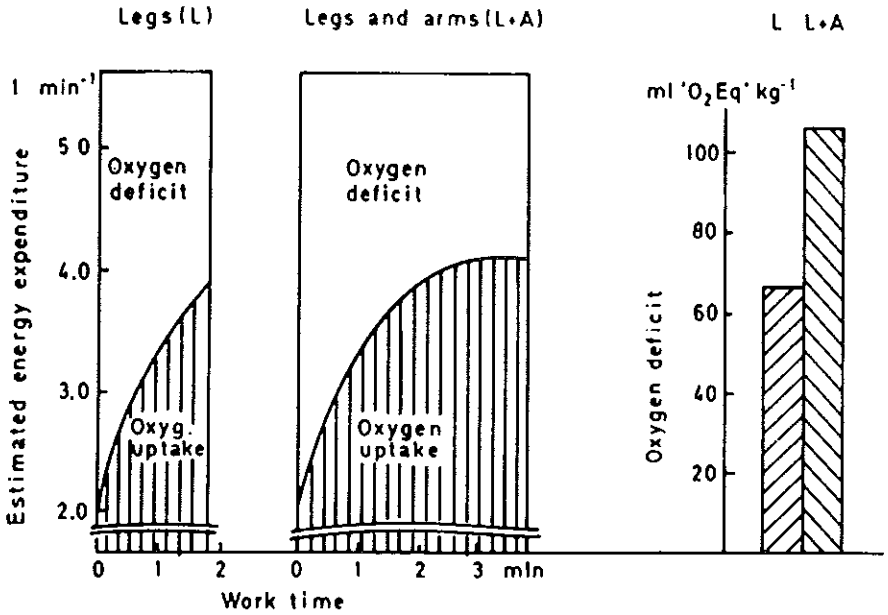

Figure 5. The oxygen uptake and the estimated oxygen deficit are illustrated when exercising with the legs (left) and with the arms and legs (right) in one subject. These data demonstrate that the fraction of the muscle mass involved in the exercise is decisive for the magnitude of the maximal oxygen deficit. Adding arms to leg bicycle exercise increased the oxygen deficit by 60-70% (6).

No measurements are available on top athletes performing whole-body exercise. Thus, the upper range for anaerobic capacity, as in successful rowers or swimmers, is presently unknown. If it is assumed that a top-class 800-m runner has the equivalent of 100 ml "O_2 eq" • kg^{-1} in anaerobic capacity while running, a top rower should have 150 ml "O_2 eq" • kg^{-1} or above in an all-out rowing performance.

Critical Contributions by Lars Hermansen

The work of Lars Hermansen has been cited frequently in the above section, and a summary of his scientific contributions is available elsewhere (78). Still, it is appropriate to briefly highlight some of Lars's investigations in the field of anaerobic capacity. What these investigations all have in common is that they were performed at a critical time and on a critical subject. Thus, in addition to the new knowledge they gave us, they initiated new thinking and complementary studies.

In the middle of the 1960s, when muscle biopsies became an acceptable procedure on healthy man, Lars took part in the first direct measurements of muscle glycogen and its utilization in exercise (26). The next significant contribution was the very first measurement of muscle pH at rest and in exhaustive work (28). This was followed by evaluating the role of a reduction in pH for force generation by muscle

fibers (17). Equally crucial were the studies of the fate of lactate in the recovery period from intense exercise. He could document that moderate exercise during recovery caused a faster elimination of lactate from the muscle, probably due to enhanced perfusion (29). Further, Lars pointed out the possibility that lactate in skeletal muscle could not only be transferred to pyruvate and oxidized but could also be used as substrate for gluconeogenesis in muscle (30). His last initiative (27), suggesting a more systematic use of the maximal oxygen deficit as a measure of anaerobic capacity, may prove to be most useful in quantifying the maximal anaerobic energy release.

Present

From the previous discussion, it is apparent that the focus has been on whole-body oxygen deficit. This is natural because it is the anaerobic energy release during ordinary exercise that has practical significance. To understand what limits anaerobic energy yield and what mechanisms are involved in its regulation, then other approaches may provide new insights. Thus, we have employed the recently developed knee-extensor exercise model, which allows for a small, well-defined muscle group to perform dynamic contractions (1), and work performed and energy turnover can be expressed per kg muscle weight. Further, precise quantitative measurements can be made of cellular events as well as substrate and gas exchange between the capillary bed and the contracting muscles (2, 77, 81).

Free Energy From ATP Hydrolysis

The exact value for the mechanical efficiency in bicycle work is unknown near or at exhaustive exercise intensities. One reason for this is the difficulty involved in estimating possible energy yield from lactate production. The principal problem is summarized in Figure 6. Oxygen uptake of the exercising muscles increases linearly with elevation in work load, higher work intensities having no tendency for the rate of increase in oxygen uptake to decrease. From the continuous release of lactate and what is accumulated in the muscle, an estimation can be made of the "theoretical" energy yield from glycolysis (Table 3). At approximately 80% of peak knee-extensor oxygen uptake, the estimated energy made available by glycolysis amounts to the equivalent of 8 ml • kg^{-1}, which is only 2% of the observed oxygen uptake. Closer to and at peak exercise, the energy release is equivalent to 56 and 95 ml • kg^{-1}, respectively, which represents 10-15% aerobic metabolism.

Should the results be interpreted to mean that mechanical efficiency is reduced in proportion to the elevation in anaerobic energy release? This is a possibility. However, a more likely explanation is that concomitant with the enhanced lactate production, there is a gradual reduction in free energy from the ATP hydrolysis. The magnitude can be estimated from the equation

$$\Delta G_{ATP} = \Delta G^{\circ}_{ATP} + Rt \cdot T \cdot \ln \left(\frac{ADP \cdot Pi}{ATP}\right),$$

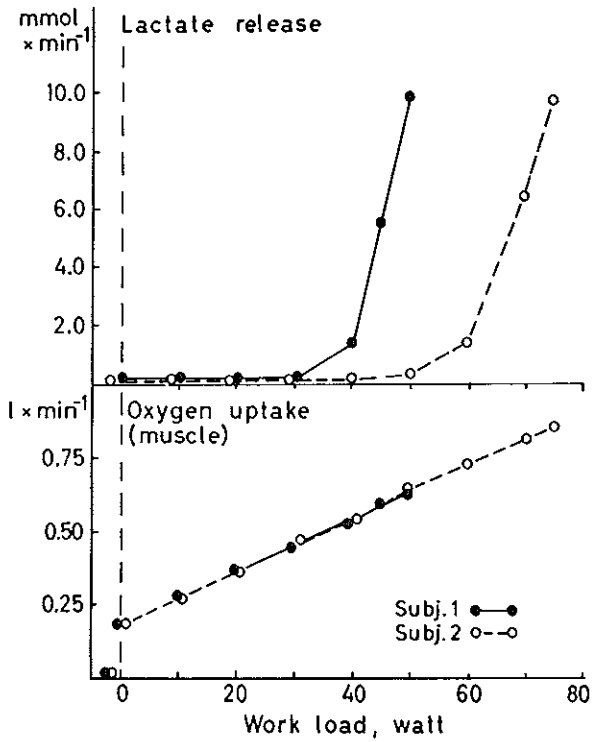

Figure 6. Oxygen uptake of the knee extensor at rest and at various work levels in two subjects with different work capacities (lower panel). The lactate release from the knee extensor is depicted in the upper panel (data are from 2, 81).

where T is the muscle temperature, Rt a constant, and ln the natural logarithm of the ratio for muscle ADP • P_i/ATP (42). Although not considered in this equation, pH influences the situation as well (14).

By introducing appropriate values for the various variables, the reduction in ΔG_{ATP} can be up to 20%. This is the case with reduction in pH to 6.5, increase in muscle temperature to 38.5° C, and an elevation in P_i to 20 mmoles • kg^{-1}, with small changes in ADP (a 2- to 4-fold increase above resting level) and ATP (10-20% reduction from rest). These estimations indicate that the drop in free energy from ATP hydrolysis could be similar in magnitude to the estimated energy obtained from anaerobic glycolysis. It should be emphasized that this in itself does not prove either estimation to be right. Further, the estimations of changes in ΔG for ATP hydrolysis with intense exercise are especially uncertain due to the lack of knowledge of whether the P_i is free or bound. Indeed, it has been suggested that ΔG_{ATP} is unaltered in spite of profound disturbance of the internal milieu (43).

If a lowering of free energy from ATP hydrolysis occurs, we can speculate why lactate is continuously produced at work intensities where the capacity for respiration would be sufficient. A possibility could be that the increased demand of pyruvate for mitochondrial usage at high relative work rates causes an overflow of pyruvate

Table 3 Data on Oxygen Uptake During Knee-Extensor Exercise at High Work Intensities and the Lactate Accumulated in the Thigh Muscles As Well As Released During the Exercise

Oxygen uptake (approx. % of peak value)	Lactate Production		Estimated energy yield from lactate production[a] (ml • min^{-1})	Observed oxygen uptake (ml • min^{-1})
	Release (approx. mmol • min^{-1})	Accumulation (mmol • kg^{-1} • min^{-1})		
80	1.5	0	8	400
90-100	5	1.5	56	540
100	9	4	95	620

Note. From refs. 2, 81.

[a]The energy yield from the lactate production is estimated (1 mol of La = 1.5 mol ATP = 5.6 L O_2).

to lactate, a view similar to the one proposed by Huckabee (58). The increase in lactate concentration causes pH to become reduced, which in turn affects the CPK reaction and elevates the P_i concentration (69). Concomitantly, heat is accumulating in the muscle, which affects ΔG_{ATP}. In this perspective the initial lactate accumulation can be viewed as the initiation of a circulus vitiosus, where diminished free energy from ATP hydrolysis via the redox stage of the cytosol contributes to enhanced glycolysis in the muscle.

Exercise Protocol

In the experiments to be reported upon, a work intensity was chosen such that exhaustion occurred in the first 8 subjects within 2-4 min. Continuous measurements of whole-body oxygen uptake were performed preexercise, during the exercise, and for the first 60 min of recovery. Blood flow in the femoral vein was measured at rest, as frequently as possible during the exercise period, and repeatedly in the recovery. Concomitantly, blood samples from the femoral artery and vein were drawn and analyzed so that thigh oxygen consumption could be determined as well as a-v_{fem} difference for lactate. In addition, muscle biopsies were taken and analyzed for lactate and pH at rest, at exhaustion, and 3 times in recovery (at 3, 10, and 60 min). Of note is that the calculations of oxygen demand, deficit, and debt are based on a constant energy yield from ATP hydrolysis and without taking into account a possible overestimation of mechanical efficiency during the exercise.

Oxygen Deficit

The resting blood flow of 0.2-0.4 L • min^{-1} increased quickly, reaching 3.0-5.0 L • min^{-1} before exhaustion. Concomitantly, the a-vO_2 difference over the leg increased, resulting in up to a 100-fold increase in muscle oxygen uptake. The total amount of oxygen utilized by the muscle during the exercise was 1.9 L. The estimated demand averaged 3.3 L, which resulted in an oxygen deficit of 1.4 L. Lactate production contributed 78% to that oxygen deficit, or the equivalent of 1.1 L of O_2.

Lactate Production

The a-v difference for lactate widened markedly during the first minute of the exercise and reached close to 4 mM at exhaustion. Total a-v lactate difference during the exercise amounted to 14.8 mmoles • kg^{-1}. In the same time period, lactate accumulated in the muscle from 1.6 to 29.2 mmoles • kg^{-1} w.w. Thus, of the approximately 45 mmoles • kg^{-1} w.w. of lactate produced, some 1/3 escaped the muscle during the exercise. The efflux of lactate was, in essence, linearly related to the elevation in muscle lactate (Figure 7). Thus, no tendency for a leveling off in lactate release from the muscle, as earlier reported by Jorfeldt et al. (36), was observed. They suggested that the lactate transport mechanisms became saturated and limited

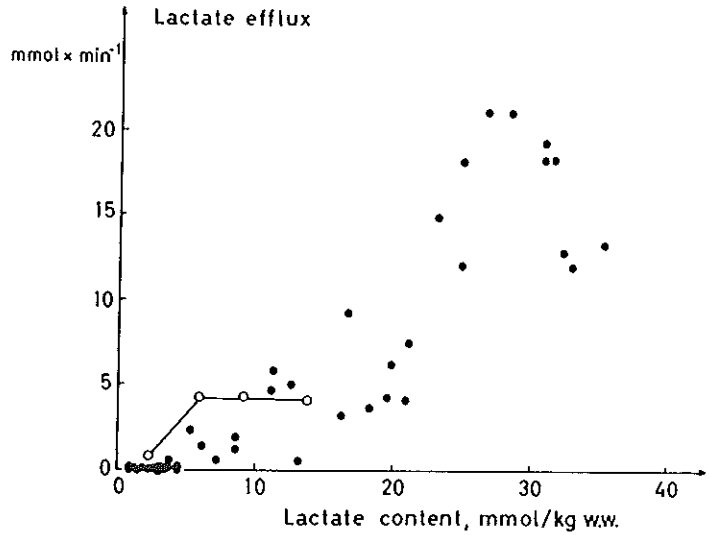

Figure 7. Individual data on 11 subjects for the release of lactate from the muscle in relation to the muscle lactate concentration. The open circles give mean values published by Jorfeldt et al. (36).

the lactate release from muscle. Our peak values for lactate release approached 20 mmoles • min^{-1}, which is 5 times higher than observed by Jorfeldt et al. (36).

The peak lactate release observed during exercise in our study most likely underestimates the release of lactate from the knee-extensor muscle to the blood. A possible explanation may be that the dominant fraction of the blood flow to the thigh muscles perfuses the knee-extensors, but some is directed to the other muscles of the thigh. As the arterial lactate concentration during the exercise becomes markedly elevated, lactate is delivered to and taken up by the hamstrings. No direct measure of lactate concentration in this muscle was performed, but the lactate concentration in the resting contralateral leg demonstrated an elevation to 5-6 mmoles • kg^{-1} w.w. A schematic illustration of likely values is depicted in Figure 8. These values indicate that the amount of lactate released from the knee extensor to the blood used in our calculations may underestimate the true release by up to 1 mmoles • min^{-1} at the end of exercise, which makes the difference between the present study and the release values of 4 mmoles • min^{-1} reported by Jorfeldt et al. (36) even larger. In the latter study, conventional bicycle exercise was performed, and it is likely that skeletal muscle blood flow was markedly lower than in the present study. Perfusion may explain the difference observed in lactate efflux in the two studies and may constitute a limitation to extrusion of lactate from muscle rather than the transport of lactate across the sarcolemma.

Does the reduced pH cause exhaustion? Force and kicking rate were monitored continuously. Either a change in the force tracing, indicating work done by the hamstring (see 1), or a drop in rate were the objective determinants for when the exercise was terminated. At this point muscle pH was reduced, but only to 6.69 (6.50-6.84). The increase in H^+ concentration that this lowering in pH represents

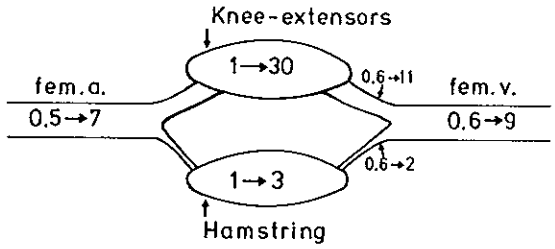

Figure 8. A schematic illustration of likely values for whole blood (artery and vein) and muscle lactate concentration (knee extensors and hamstring) at rest (first value given) and at exhaustion (second value, after the arrow). For further explanation, see the text.

could be associated with impaired ability for force generation (17). In 2 of the subjects, the exercise was repeated after 60 min of recovery. Muscle lactate concentration did not reach as high a level as in the first work bout, and the reduction in pH was only 0.25 units (to 6.79), or 0.10 units less than after the first exercise. This finding and the fact that there was a large variation in muscle pH found among the subjects at exhaustion favor the notion that factors other than muscle pH should be considered as the causes of fatigue and inability to perform at the given exercise intensity. Further, the effect of the lower pH on retarding the rate of glycolysis also appears to be small. Also, ATP resynthesis is probably not a limitation because its concentration in muscle at exhaustion is only slightly below that observed at rest.

Gradients for Lactate

Prior to exercise almost no gradients for lactate in the water phases of muscle cell (interstitial space), plasma, and red blood cells are apparent (Table 4). During exercise the pattern quickly changes. Of note is that there is a gradient not only between muscle and plasma but also in blood between plasma and the red blood cells. This is due to a slow, facilitated diffusion of lactate through the membrane of erythrocytes (only 5% of the lactate enters the red blood cells by simple diffusion; Figure 9). The lactate uptake by red blood cells is so slow that there still is a pronounced difference in lactate concentration in the arterial blood as late as 3 min into the recovery. At the end of exercise, femoral vein plasma concentration of lactate is only half of what is accumulated in the muscle, or 18 mmoles • L^{-1}, but 3 min into recovery, the difference was reduced to 5 mmoles • L^{-1}, and it was nil after 10 min of recovery (Table 4).

Recovery Lactate Efflux

The results in Table 4 demonstrate that the lactate concentration in muscle at the end of the exercise has returned to the normal resting value within 1 hour. The three main routes for the muscle lactate clearance are (a) release into the capillary bed, (b) conversion to pyruvate, and then (c) either oxidation or further conversion to other compounds. Of these three possibilities, we have data for the first because

blood flow and a-v difference for lactate over the leg was followed during the 60 min of recovery. The most striking finding is that as much as 82% of the lactate left the muscle as lactate via the blood stream.

Table 4 The Concentration of Lactate in Muscle of the Vastus Lateralis and Femoral Vein Blood at Rest, at End of Exhaustive Exercise, and at Various Times in Recovery

Condition	Gradient For Lactate (mmol • L^{-1})		
	Muscle[a]	Plasma[b]	Erythrocytes[b]
Rest	1.8	1.6	1.6
Exercise	36.2	18.4	12.0
Recovery			
3 min	18.8	13.8	11.0
10 min	9.9	9.0	8.0
60 min	1.8	1.9	1.9

Note. Based on water content of muscle tissue and likely values for its distribution between intra- and extracellular compartments (81) as well as that of plasma and erythrocytes.

[a]Vastus lateralis. [b]Femoral vein.

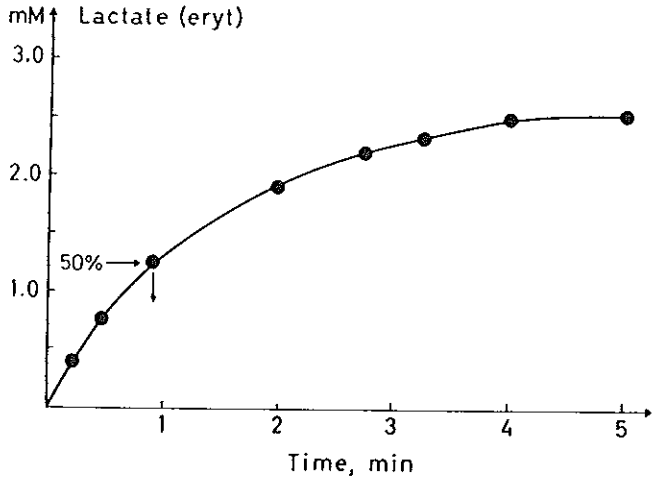

Figure 9. Lactate concentration of erythrocytes (mmol/L cells) in relation to the time the blood cells have been incubated in a solution containing 4.4 mM lactate. The cells were depleted of ATP by preincubation with iodoacetomide and inosin in order to reduce endogenous lactate production (courtesy of L.O. Simonsen and C. Juel, unpublished data).

Oxygen Deficit and Debt

It can be stated that the oxygen deficit measured in the leg was of the same magnitude as that for the whole body. Further, in recovery the whole-body oxygen debt was markedly larger than the debt found for the leg. This finding is in agreement with the observations that most lactate leaves the muscle in recovery and that the extra energy for the metabolism of lactate is located outside the muscle performing the exercise. The magnitude of the oxygen debt observed for the leg is most likely due to the resynthesis of ATP and CP and the saturation of myoglobin/hemoglobin, which is estimated at 0.5-0.6 L.

Magnitude of the Anaerobic Capacity

The present subjects achieved a maximal oxygen deficit equivalent to from 0.34 to 0.68 L O_2 • kg^{-1} muscle. The human body consists of 40% muscle; some 10-12 L O_2 Eq • kg^{-1} b.w. would then be a reasonable estimate for the maximal oxygen deficit of a sedentary person. A rower with both a larger body weight and a larger muscle mass fraction would be anticipated to achieve perhaps 15 or 20 L O_2 Eq • kg^{-1} b.w. In this context the values for maximal oxygen deficit summarized in Table 2 are noteworthy. They are at most only 1/2-2/3 of the estimated values above. Some recent determinations in rowers indicated that they also are far from reaching the anticipated values. One reason for this is that not all muscles or portions of muscle are engaged in the exercise—not even in rowing—to the limit of the athlete's anaerobic capacity. In addition, the perfusion of the muscle plays a major role for the maximum amount of lactate that is cleared from the muscle during the exercise. In the present experiment when the perfusion was high, it amounted to 30-40% of the lactate produced. Thus, the muscle lactate clearance is a function of the amount of muscle involved in the exercise. If a muscle mass larger than the quadriceps is engaged in the exercise, optimal perfusion of the muscle cannot be achieved because the peripheral blood flow is limited centrally (2, 72). Thus, the larger the muscle mass involved in the exercise, the smaller the fraction of the lactate produced that can leave the muscle (Figure 10).

Prospective

Free Energy From ATP Hydrolysis

In the description of the present results, we have not accounted for a possible alteration in energy release by ATP hydrolysis during short-term exercise to exhaustion. It has been suggested that up to a 20% reduction in free energy may occur. Whether it does or not is unclear. This is a critical question because it affects the estimate of the ATP turnover and, thus, the maximal oxygen deficit. The answer may also give clues to understanding what initiates lactic acid production during exercise.

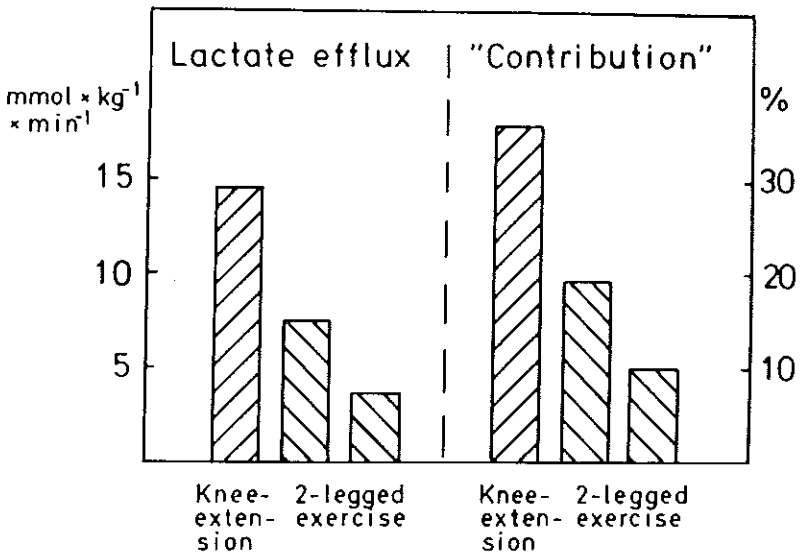

Figure 10. Mean values for the lactate efflux in the present study (knee extension) and two studies in the literature in which ordinary bicycle work has been performed (36, 41). To the right is estimated the relative "contribution" of the efflux of the total lactate production during the exercise.

Can an answer be found? An approach similar to the one used by Edwards may give some insight (19). His subjects performed intense static contraction with the knee extensors. As the circulation through the muscle was arrested, heat accumulated in the muscle. A precise measure of the heat content and the time course for its change during a steady contraction, coupled with detailed measurements of energy utilization, could provide an answer as to whether less energy becomes available from the ATP hydrolysis in the late, as compared to the initial, phase of contraction.

Regulation of Glycolytic Rate

Regarding the question of how fast the anaerobic capacity can be utilized, the factors regulating the rate of glycolysis have provoked special interest. The approach so far has been to measure various compounds and make estimates of free and bound concentrations of key regulators. This approach has its limitations. However, if properly matched with the application of NMR technology, which allows for direct measurements of the free concentrations of some of these compounds, a major breakthrough is possible. A problem that will remain is compartmentalization, where especially cytoplasmic versus mitochondrial concentrations of ADP/ATP and NAD/NADH are critical (23). Mitochondrial volume of muscle fibers can vary from a few to 10-12 volume %, as a function of fiber type and training status (see 75). By careful selection of muscles for study (for example m. soleus and m. gastrocnemius), some insight may be gained on an otherwise difficult problem.

Extrusion of Protons and Lactate

The evidence for a facilitated diffusion of both hydrogen ions and lactate (37), which in part may be a cotransport, is overwhelming (37). However, contrasting views are held (24). A final resolution of this question is a prerequisite to understanding which factors may limit the efflux of lactate from the muscles. It also has a bearing on the pH regulation of muscle cells, although the buffering capacity of the muscle is equally critical. By applying techniques used on other tissues, we may find some answers. For example, by applying inhibitors of facilitated diffusion of lactate and H^+, known to have an effect in erythrocytes (see 15), to isolated muscle fiber preparations, a quantitative description of the transport route(s) in the sarcolemma would be available. If the transport is facilitated, the identification of the mechanisms for transport will give the basis for quantification of flux rates. In turn, this will constitute a basis for evaluation of whether such mechanism(s) may saturate during in vivo exercise. The special problem of the functional significance of muscle perfusion for the lactate and H^+ release can be studied in an isolated, in vitro muscle preparation, where the activation of the muscle, as well as the blood flow, is controlled.

What Is the Cause of Exhaustion?

This question has been raised repeatedly in this century (see 67). As soon as a more universal factor has been proposed to be a likely candidate, it can be shown that the compound or mechanism may be at work only in special circumstances or may co-vary with other candidates which are related to fatigue and exhaustion. As in earlier studies with the knee-extensor model (81), pH is not reduced to a very low level in spite of quite high muscle lactate concentrations. In the investigations of Donaldson et al. (17, 18), a pH of 6.5 at a given Ca^{2+} concentration markedly affected tension development of fast-twitch (FT) fibers, whereas slow-twitch (ST) fibers were affected to a lesser extent. At a pH of 6.7-6.8, as in this study, the pH effect should be minor, especially with an increased activation rate of the motor units resulting in elevated free Ca^{2+} concentration, which could compensate for a reduced pH. However, it may also be argued that the total force developed by the knee-extensor muscle in each contraction represents an unusually large fraction of its force capacity. This may demand a dominant percentage of the available motor unit pool to be recruited at a high rate already at onset of the exercise. As a result, the performance of the muscle is more sensitive to quite small reductions in the peak force development of individual fibers; other fibers cannot compensate because firing rate is already optimal.

What are the critical experiments to be performed? First, we should evaluate whether or not the fatigue is central. This can be investigated by direct electrical stimulation of the muscle at the point of exhaustion. If the fatigue is beyond the motor end plate, sophisticated EMG analyses could be used to evaluate the impairment of propagation of the action potential, including possible alterations of frequency of activation. However, technique problems would probably be encountered, limiting the success of this approach. Electron probe spectra, combined with identifying the location at the ultrastructural level, could reveal ion changes in the T tubuli system, lack of activation, or malfunction of the SR system.

Adaptation

The following brief comments on adaptation are based on speculations on what limits anaerobic work capacity. Various possibilities are outlined in Table 5.

Ad 1. The observed large variation in the time for complete utilization of a person's maximal oxygen deficit may point to the rate of glycolysis as a limitation. A high muscle glycogen content has been shown by some to affect the rate of glycolysis (9, 44), but the results of this study as well as earlier data fail to support this notion (25). Above a certain critical level of muscle glycogen, a further elevation in glycogen has only a little significance on lactate production.

Increase of glycolytic enzymes, including LDH_{4-5}, may be more important. An increase in glycolytic enzymes may reduce the effect of the accumulation of inhibitors such as pH, IMP, and so on, causing better maintenance of the glycolytic rate (22). Can training directly affect the regulators of the glycolytic rate? If Newsholme (64) is correct that the sympathetic nervous system has a significant effect via substrate cycling, then there is a possibility of a training effect.

Ad 2. Several investigations have shown that the buffering capacity of sprint-trained subjects is higher than that of sedentary men (70, 80). Why this is the case is less clear (66). In addition to the role of the CP content and its utilization, none of the protein fractions have definitively been linked with the capacity of muscle to buffer H^+. The role of the bicarbonate system is probably of little significance in muscle (68). Can training cause an improved tolerance to a lowering of muscle pH, as has been suggested (25)? The result of such an adaptation would be that a given drop in pH would cause less impairment of metabolism and force generation. A specifically trained person would then have a lower pH at exhaustion, which has been reported for blood pH but not yet for muscle pH (25).

Ad 3. The present data did not show a decline in efflux rate of lactate at the highest muscle lactate concentration, suggesting that lactate transport mechanisms are sufficient and do not constitute a limitation.

Ad 4. It has been suggested that some fibers within an intensely contracting muscle not only take up lactate from adjacent, more active muscle fibers but are capable of metabolizing the lactate during the exercise (10). The practical role of this pathway is probably negligible. The basis for this statement is that at very intense exercise, most fibers of a muscle would be recruited. This is especially true for the slow-twitch fibers, which have the largest potential for metabolizing lactate. However, these fibers are also quite capable of producing lactate themselves. Thus, the possibility of transfer of lactate within an intensely contracting muscle from a producing fiber to a clearance fiber is mainly of theoretical interest.

Ad 5. Of much greater importance is the clearance of the lactate through the interstitial space into the capillary bed and blood. Of note is that an improvement of this transfer route is the result of pure aerobic-type training.

From the above discussion, it should be clear that there may be two modes of training to improve anaerobic capacity. One is to obtain the highest possible rate of glycolysis, and the other is to maintain the work rate in the face of increasing lactate production. The optimal training pattern may be different for these two variables. Speed and intensity are essential elements for training the rate of glycolysis. The duration of the effort is probably more important for handling the lactate. In this context, it is worthwhile noticing that patients with intermittent claudication do not have a high glycolytic potential in their calf muscles (71), probably because their

Table 5 Schematic Summary of Factors Related to the Lactate Production and the Fate of Produced Lactate in Skeletal Muscle During Exhaustive Exercise

Event	Limiting Factor	Adaptation
Rate of glycolysis and lactate production	Glycogen, key activators, LDH_{4-5}	Elevation of glycogen storage, enhanced glycolytic enzyme content including LDH_{4-5}, enhanced activation/less inhibition
Accumulation in the muscle fiber	Buffer capacity, pH tolerance	Increased breakdown of CP, elevation of specific amino acids
Transport (if facilitated)	Number of lactate transporters	Increased number of lactate transporters
Uptake by adjacent muscle fibers (FT ⟶ ST fibers)	"Own" pyruvate and lactate formation, LDH_{1-2}, mitochondrial capacity, NAD:NADH ratio	Enhanced oxygenation of less active adjacent fibers, enhanced oxidative potential and LDH_{1-2}.
Disappearance via interstitial space and blood	Capillary density, muscle perfusion, uptake by other tissues	Capillary proliferation, improved central circulatory capacity, enhanced oxidative potential of nonexercising tissues

walking speed is not a sufficient challenge to glycolytic metabolism. Further, their anaerobic work capacity is low due to a very minor lactate efflux from the muscles because the perfusion of the leg muscles is also low. This is in contrast to athletic training at altitude or hypoxic training. Both procedures appear to result in a pronounced improvement in anaerobic work capacity (62, 63, 82). Maybe "hypoxic" training is more effective than training at sea level.

Conclusion

This presentation is dedicated to the memory of Lars Hermansen. For those of us who were fortunate enough to have known him and to have been close to him, we know what an able and very friendly person he was. Lars could also stimulate and inspire—not only the colleagues in his own laboratory but also the audiences at meetings as well as other investigators in his field of research. Thus, the study we have performed in our laboratory has been initiated solely due to Lars's convincing suggestion that the old problem of oxygen deficit and debt is worth reexamining. I think that the ongoing investigations in Oslo on the anaerobic energy release in exhaustive muscular exercise by Medbø and colleagues demonstrate that he was correct. Hopefully, our efforts on the same subjects will also prove useful.

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