Review article

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PHYSIOLOGICAL BACKGROUND OF THE CHANGE POINT IN $\dot{V}O_2$ AND THE SLOW COMPONENT OF OXYGEN UPTAKE KINETICS

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It is generally believed that oxygen uptake during incremental exercise — until $\dot{V}O_{2max}$, increases linearly with power output (see eg. Astrand & Rodahl, 1986). On the other hand, it is well established that the oxygen uptake reaches a steady state only during a low power output exercise, but during a high power output exercise, performed above the lactate threshold (LT), the oxygen uptake shows a continuous increase until the end of the exercise. This effect has been called the slow component of $\dot{V}O_2$ kinetics (Whipp & Wasserman, 1972). The presence of a slow component in $\dot{V}O_2$ kinetics implies that during an incremental exercise test, after the LT has been exceeded, the $\dot{V}O_2$ to power output relationship has to become curvilinear. Indeed, it has recently been shown that during the incremental exercise, the exceeding of the power output, at which blood lactate begins to accumulate (LT), causes a non-proportional increase in $\dot{V}O_2$ (Zoladz *et al.* 1995) which indicates a drop in muscle mechanical efficiency. The power output at which $\dot{V}O_2$ starts to rise non-proportionally to the power output has been called "the change point in $\dot{V}O_2$" (Zoladz *et al.* 1998). In this paper, the significance of the factors most likely involved in the physiological mechanism responsible for the change point in oxygen uptake (CP-$\dot{V}O_2$) and for the slow component of $\dot{V}O_2$ kinetics, including: increase of activation of additional muscle groups, intensification of the respiratory muscle activity, recruitment of type II muscle fibres, increase of muscle temperature, increase of the basal metabolic rate, lactate and hydrogen ion accumulation, proton leak through the inner mitochondrial membrane, slipping of the ATP synthase and a decrease in the cytosolic phosphorylation potential, are discussed.
Finally, an original own model describing the sequence of events leading to the non-proportional increase of oxygen cost of work at a high exercise intensity is presented.

Key words: *acid-base status, exercise, muscle fatigue, oxygen uptake, power output, slow component of oxygen uptake kinetics.*

INTRODUCTON

It is generally believed that the oxygen uptake ($\dot{V}O_2$) during incremental exercise — until $\dot{V}O_{2max}$, increases linearly with the power output (PO) (1—3). On the other hand, it is well established that the oxygen uptake reaches a steady state only during a low power output exercise, but during a high power output exercise, performed above the lactate threshold (LT), the oxygen uptake shows a continuous increase until the end of the exercise. This effect has been called by Whipp & Wasserman (ref. 37), the slow component of $\dot{V}O_2$ kinetics (for review see 4).

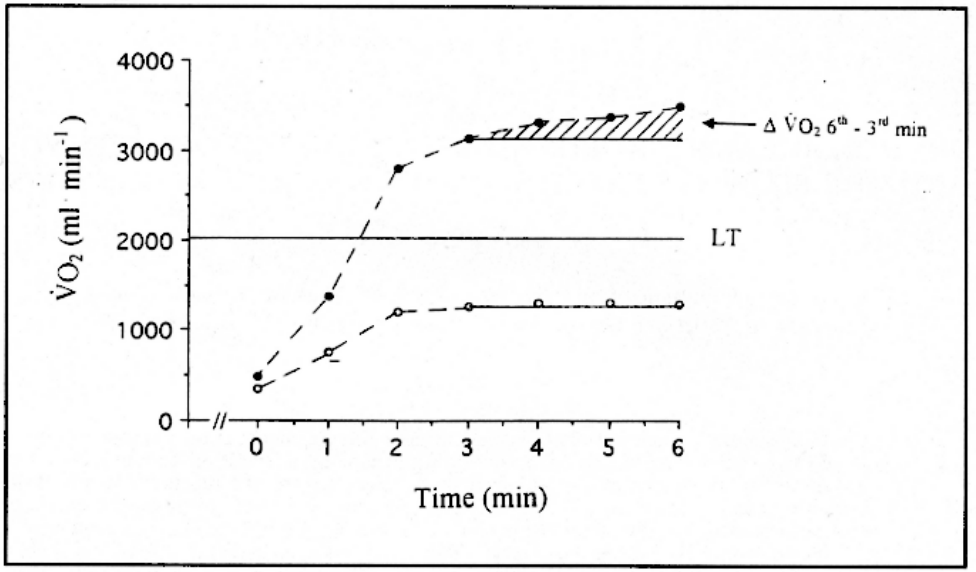

Fig. 1. The oxygen uptake ($\dot{V}O_2$) reached during cycling exercise below (o) and above (•) the lactate threshold (LT). Note the appearance of the slow component of $\dot{V}O_2$ kinetics, expressed as the differences in $\dot{V}O_2$ between the 6th and the 3rd minute of work (Δ $\dot{V}O_2$ 6th—3rd min) during cycling exercise performed above the LT.

The presence of the slow component in $\dot{V}O_2$ kinetics implies that during incremental exercise test, after the LT has been exceeded, the $\dot{V}O_2$ to power output relationship has to become curvilinear.

Indeed, it has recently been shown and confirmed in several studies (5—7) that during the incremental exercise, exceeding of the power output at which blood lactate begins to accumulate (lactate threshold) causes a non-proportional increase in $\dot{V}O_2$. This increase in $\dot{V}O_2$ clearly indicate a drop in muscle mechanical efficiency. The power output at which $\dot{V}O_2$ starts to rise non-proportionally to the power output has been called "the change point in $\dot{V}O_2$" (CP-$\dot{V}O_2$) (8, 9) (see *Fig. 2*).

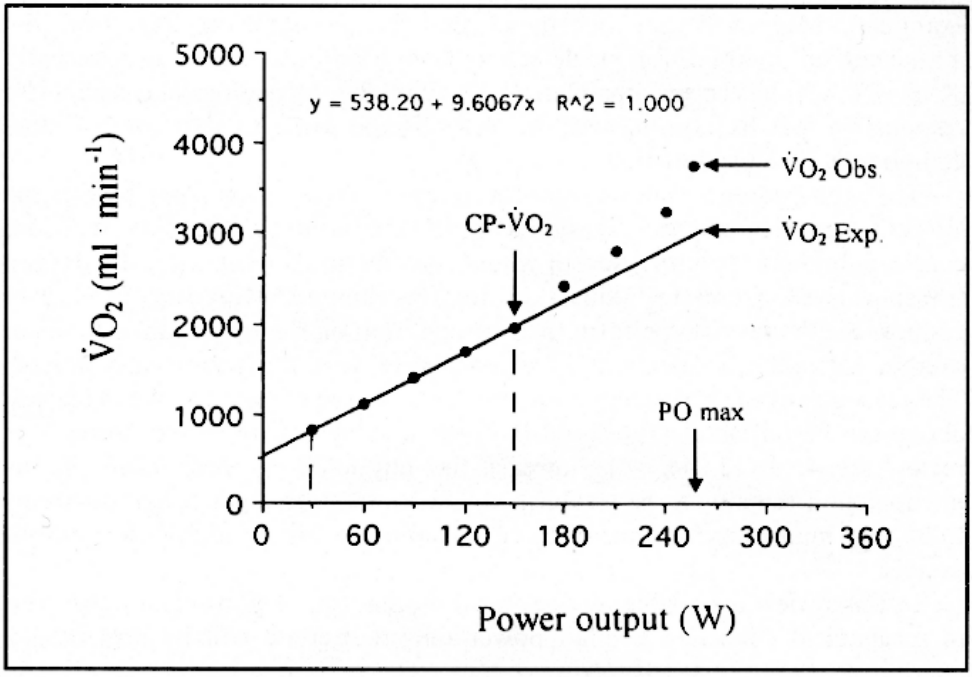

Fig. 2. The individual data of the oxygen uptake ($\dot{V}O_2$) during the incremental power output exercise test, and the example of calculating the expected oxygen uptake at the maximal power output ($\dot{V}O_2$ Exp.) The linear regression is based on the 3rd minute data of the $\dot{V}O_2$ reached at the stages up to the change point in $\dot{V}O_2$ (CP-$\dot{V}O_2$), (for details see ref. 9). Note the difference between the maximal oxygen uptake ($\dot{V}O_{2max}$) reached during this test ($\dot{V}O_2$ Obs.) at maximal power output (PO max) and the expected oxygen uptake at the maximal power output ($\dot{V}O_2$ Exp.)

The magnitude of the drop in muscle mechanical efficiency during the incremental exercise test may be judged by the difference in the oxygen uptake reached in the final stage of the test and the expected $\dot{V}O_2$ at the maximal power output (PO max), calculated on the basis of the linear relationship between $\dot{V}O_2$ — power output, derived from the data below the lactate threshold (see *Fig. 2*). As reported in the recent studies (6, 7, 9) the drop in mechanical efficiency calculated in this way (difference between the measured and the expected $\dot{V}O_2$ at the PO max amounts to 16—20 percent of the expected value (see also *Fig. 2*).

As already pointed out by Zoladz *et al.* (6) a non-linear relationship between $\dot{V}O_2$ and power output in incremental tests has been documented previously (10, 11) but the significance and underlying mechanisms of these observations has not been widely recognised or systematically investigated. Furthermore, in neither of these earlier reports, the onset of the extra $\dot{V}O_2$ per watt of heavy work in relation to the onset of blood lactate accumulation was

examined. Moreover the concept of the change point in $\dot{V}O_2$ and the mathematical method for it detection has been introduced just recently (8, 9, 71). It has been postulated (7) that the physiological mechanism responsible for the non-linearity in $\dot{V}O_2$ is the same as that for the slow component of $\dot{V}O_2$ kinetics.

The non-proportional increase of oxygen uptake occurring above the CP-$\dot{V}O_2$ seems to be specially significant in case of the patients suffering from cardio-pulmonary insufficiency, in whom the functional reserves of the oxygen transport system and O_2 utilisation are very limited. Moreover, in case of endurance athletes who perform their competition on the edge of their limits of exercise tolerance, an increase of oxygen cost of work may cause early fatigue. The reason(s) of the non-proportional increase of the oxygen uptake occurring above the blood lactate threshold (LT) are a subject of intensive studies (for review see 4, 9, 12, 44, 46), however the physiological mechanism of this phenomenon remains to be established. Understanding this mechanism seems to be very important for improving of the ability to sustain high power output exercise.

In this review a possible physiological mechanism responsible for the drop of mechanical efficiency at high power output exercise will be presented.

THE PHYSIOLOGICAL FACTORS INVOLVED IN THE DROP OF MUSCLE MECHANICAL EFFICIENCY AT HIGH POWER OUTPUT EXERCISE

Although, as presented above, the decrease in muscle mechanical efficiency observed at high power output exercise is a well documented phenomenon, the underlying physiological mechanism is not understood. A number of factors, including: increase of pulmonary ventilation, blood lactate and H^+ accumulation, hypercatecholaminemia, increase of muscle temperature, recruitment of type II muscle fibres, *etc.*, have been postulated to play an important role in this mechanism (for review see 4, 9, 12, 44). In this section, the most likely reasons for the decrease in muscle efficiency at high power output exercise will be discussed.

Activation of additional muscle groups

Perhaps the simplest explanation of the pulmonary slow component of pulmonary $\dot{V}O_2$ kinetics and the origin of the CP-$\dot{V}O_2$, one may suggest, is an increase of oxygen uptake in additional muscles, such as those responsible for the stabilisation of body posture, or increase of the cost of the respiratory muscles due to the intensification of the exercise hyperpnea (13). Yet, in two independent studies, the slow component of $\dot{V}O_2$ kinetics (14) and the non-linearity in

$\dot{V}O_2$: PO relationship which, as may be seen in the data by Kim *et al.* (15), have been demonstrated not only in the pulmonary $\dot{V}O_2$ but also at the level of the exercising leg muscles. Poole *et al.* (14) who have simultaneously measured the pulmonary $\dot{V}O_2$ and the leg muscle $\dot{V}O_2$ during a constant high power exercise, have shown that 86% of the increase in the pulmonary $\dot{V}O_2$ observed between the 3rd and 21st minute of cycling was attributable to the exercising muscles in the legs. This suggests that indeed most of the additional increase in $\dot{V}O_2$ represents the drop of efficiency of the working locomotory muscle cells. Moreover, in the study by Kim *et al.* (15) it could be seen that the leg oxygen uptake measured during the incremental one-legged dynamic knee extension exercise, above the power output of 30 W starts to rise non-linearly, and the $\dot{V}O_2$ / PO ratio of the final stage of the test is substantially higher than in the initial stage of the test.

The above discussed results (14, 15) give good evidence to believe that the origin of the non-linear pulmonary $\dot{V}O_2$ takes place in the working locomotory muscles. Nevertheless, at least during the cycling exercise activation of an additional muscle groups (posture stabilising muscles, arms muscles and respiratory muscles) may, to a certain degree, contribute to the non-proportional increase in the pulmonary $\dot{V}O_2$ observed above the CP-$\dot{V}O_2$.

Intensification of the respiratory muscle activity

The slow component of $\dot{V}O_2$ kinetics and the change point in $\dot{V}O_2$ are closely related to the lactate threshold (4, 8, 9). Therefore one may expect that the increase in pulmonary ventilation, which occurs above the lactate threshold, could potentially contribute to the observed drop in muscle efficiency. We have found that during the maximal cycling incremental exercise, an increase of power output from the lactate threshold level to the maximal power output was accompanied by an increase of the pulmonary ventilation from 49.6 ± 7.3 to 116.8 ± 8.9 l · min^{-1} (7). On the basis of the data reported by Aaron *et al.* (16), one may calculate that such an elevation of $\dot{V}_E$ would increase the respiratory muscle $\dot{V}O_2$ by ~ 200 ml · min^{-1}. This estimation would suggest that in our study about 1/3 of the additional $\dot{V}O_2$ (569 ± 269 ml · min^{-1}) observed at the maximal power output could be due to intensification of the exercise hyperpnoe. Yet, during constant power output exercise of lower intensities (77% $\dot{V}O_{2max}$), the contribution of the cost of the pulmonary ventilation to the slow component of $\dot{V}O_2$ kinetics was reported to be far lower (17).

Recruitment of type II muscle fibres

Recently, recruitment of type II muscle fibres has been considered as a possible cause of the slow component of the $\dot{V}O_2$ kinetics (for review see 4). This is in line with the early observations showing that individuals possessing

a higher proportion of type II muscle fibres during cycling at a given power output, utilise substantially more oxygen, when compared to a subject with a low percentage of type II muscle fibres (18). On the other hand, it is contradicted by the data from Medbo (19), who postulates that there is no difference in the mechanical efficiency of type I and type II muscle fibres during cycling exercise.

Interestingly, it has been reported that during cycling at a given power output, an increase of pedalling rate from 40 to 100 rev $\cdot$ min^{-1} has a little effect of the oxygen cost of cycling, but cycling at 120 rev $\cdot$ min^{-1} requires substantially more oxygen than 100 rev $\cdot$ min^{-1} (see 5, 20). Since such a high pedalling rate as 120 rev $\cdot$ min^{-1} is for a normal subject an optimal pedalling frequency for generating a maximal power output (21) and type II muscle fibres contribute most to the maximal power output, one can speculate that the high oxygen cost of cycling at 120 rev $\cdot$ min^{-1} may be due to a greater recruitment of type II muscle fibres.

More direct evidence supporting the hypothesis that the recruitment of type II muscle fibres contribute to the increase of $\dot{V}O_2/PO$ ratio comes from the experiments in which selective blocking of type I muscle fibres was obtained by administration of a low dosage of tubocurarine (22). This study has shown a significantly higher oxygen cost of cycling at a given power output at a pedalling rate of 60 rev $\cdot$ min^{-1} after the administration of an appropriate dose of tubocurarine, when compared to control conditions (22).

Relatively little is known about the hierarchy of recruitment of different types of muscle fibres during incremental exercise. The available data suggest that there is a progressive increase of involvement of type IIA, followed by a greater recruitment of type IIB muscle fibres when the power output increases (21, 23, 24). If indeed this is the case, then the additional recruitment of type II muscle fibres above the LT, could contribute to the additional increase of the oxygen uptake above the CP-$\dot{V}O_2$, as shown in *Fig. 2.*

It was postulated that the main reason for a lower efficiency of type II muscle fibres (expressed by the high energy phosphate produced per oxygen molecule consumed — P/O) is the efficiency of mitochondria in type II muscle fibres appear to be lower than those from type I muscle fibres (25). On the other hand, although type II muscle fibres have less efficient mitochondria, they probably produce a greater fraction of ATP in anaerobic glycolysis (which is not accompanied by oxygen consumption) than type I muscle fibres. This increases the overall P/O ratio in type II muscle fibres and counteracts the decrease in the P/O ratio caused by less efficient mitochondria. Therefore, it is not clear if type II muscle fibres have indeed a lower overall P/O ratio than type I muscle fibres. Moreover, in view of some well designed experiments there are evidence of recruitment of some of the type II muscle fibres already at a very low exercise intensity (30% $\dot{V}O_{2max}$, see Gollnick *et al.* (26) at which

normally no slow component of the $\dot{V}O_2$ kinetics is reported. Additionally, as reported by Ivy *et al.* (27) "*... a substantial percent of type II muscle fibers are activated before the lactate threshold....* ". Again, no slow component of $\dot{V}O_2$ kinetics or the change point in $\dot{V}O_2$: power output relationship has been reported during exercise performed below the lactate threshold (*Fig. 1, 2*), (for review see 4, 9, 12, 44, 46, 71). Therefore, one may question the role of type II muscle fibre recruitment in origin of the slow component of $\dot{V}O_2$ kinetics and the change point in $\dot{V}O_2$. Further studies are needed to explain the effect of type II muscle fibre recruitment on the $\dot{V}O_2/PO$ ratio at high exercise intensities.

Increase of muscle temperature

In the view of earlier studies, a rise of muscle temperature may increase the oxygen uptake by uncoupling muscle mitochondria (see e.g. 25). Based on the previous studies (28, 29), it has been postulated that an increase of muscle temperature by 3—4°C during exercise, which requires about 3000 ml $O_2 \cdot min^{-1}$, may account for a slow component of the $\dot{V}O_2$ kinetics of $\sim$300 ml $\cdot$ l^{-1} (25).

It is well documented that during intense exercise, muscle temperature may rise within a few minutes by 3—5°C (see e.g. 24, 30). Such an increase of the muscle temperature seems to be high enough to affect functioning of the mitochondria and develop a need for "additional" oxygen uptake. However, in the literature data there is no clear evidence that the increased muscle temperature increases the oxygen cost at high power output exercise. For example, Koga *et al.* (31) have reported no effect of increased muscle temperature on the slow component of $\dot{V}O_2$ kinetics. On the other hand, recent data by Ferguson *et al.* (32) have shown a higher oxygen cost of cycling at 60 rev $\cdot$ min^{-1} after pre-exercise muscle heating when compared to the control conditions. This effect is believed *"to be due to an acute transformation of type I muscle fibres towards faster properties, such that they are no longer operating at and around their optimum velocity for maximum mechanical efficiency"* (32).

Increase of the basal metabolic rate

Among the factors potentially involved in the mechanism responsible for the slow component of $\dot{V}O_2$ kinetics, one should also include an up-ward drift in the basal metabolic rate of the body occurring during high intensity exercise. An increase of the whole body temperature may affect the efficiency and metabolism of different organs and contribute to an increase of the oxygen cost of work. The recent study by Zoladz (33) supports this hypothesis. It has been shown that during a multistage incremental exercise protocol, consisting of five

bouts of cycling lasting six minute each, separated by six-minute pauses, the magnitude of the slow component of $\dot{V}O_2$ kinetics ($\Delta\dot{V}O_2^{6-3min}$) was positively correlated ($r_{xy} = 0.43$, $P<0.001$) with an increase of the pre-exercise $\dot{V}O_2$. This suggests that indeed an increase in the basal metabolic rate may contribute to the increase of the oxygen cost of work at high power output exercise as illustrated by the slow component of $\dot{V}O_2$ kinetics and the CP-$\dot{V}O_2$ present during the incremental exercise test.

Lactate and hydrogen ion accumulation

In several studies, a close relationship between the increase of blood lactate accumulation and the magnitude of the slow component of $\dot{V}O_2$ kinetics has been reported (34, 35, 36). This is perhaps the reason why so much attention has been paid to acidosis as a possible cause of the slow component of $\dot{V}O_2$ kinetics (13, 34, 37). Moreover, the change point in the oxygen uptake (CP-$\dot{V}O_2$) (*Fig. 2*) observed during an incremental exercise test occurs at the PO very similar to the lactate threshold (8, 9, 71). Despite the fact that, as reported in a number of studies (for review see 4, 38), the presence of the slow component of the $\dot{V}O_2$ kinetics is always accompanied by a significant increase in blood lactate accumulation, and an increased blood H^+ concentration, it still remains unclear to what degree, if at all, the rise of blood lactate concentration and the increase of blood H^+ modulate the slow component of $\dot{V}O_2$ kinetics.

According to Stringer *et al.* (39), metabolic acidosis may contribute to the increase of the slow component of $\dot{V}O_2$ kinetics by a shift of the oxyhemoglobin dissociation curve to the right and increase oxygen transport to the muscle and promote aerobic metabolism during heavy exercise. Yet, this concept implies that the delivery of oxygen to the muscle controls significantly the rate of oxygen consumption at low power outputs (below the change point and lactate threshold). This does not seem to be likely because of the very low value of the K_m constant of mitochondrial respiration for oxygen. Therefore, the above presented explanation by Stringer *et al.* (39) seems to be doubtful, unless it is demonstrated experimentally that oxygen concentration in "slowly" — working muscle approaches the K_m constant.

Capelli *et al.* (40) has suggested that intramuscular H^+ accumulation may be responsible for the slow component of the $\dot{V}O_2$ kinetics by increasing free creatine concentration (41). The increase of free creatine may be caused by a shift in the equilibrium of the creatine kinase reaction due to H^+ accumulation ($H^+ + ADP + PCr \Leftrightarrow ATP + Cr$), (42). However, so far there has been no evidence from *in vivo* study to confirm this possible explanation. Furthermore, the creatine production does not stimulate the mitochondrial respiration by itself, but possibly only via phosphate production. Moreover, the shift of the creatine kinase reaction towards creatine production leads also to

an increase in the ATP/ADP ratio, which can be expected to inhibit oxygen consumption. For this reason, the relevance of the mechanism proposed by Capelli and co-workers (40) needs more studying.

In theory, since a proton is one of the reagents in the ATP synthesis/splitting reactions, one may consider a direct effect of H^+ on the phosphorylation potential. However, the ability of mitochondria to fast recreation of the initial phosphorylation potential, changed by variation in pH, through changes in the ATP/ADP ratio, questions the relevance of this mechanism in originating the slow component of $\dot{V}O_2$ kinetics.

Recently, it has been shown that pre-exercise acidification, induced by ingestion of ammonium chloride (3 $mmol \cdot kg^{-1}$ BM), was accompanied by a significant increase of the magnitude of the slow component of $\dot{V}O_2$ kinetics in humans (43, 44). This suggests that, indeed, enhanced metabolic non-organic acidosis increases the magnitude of the slow component of oxygen uptake kinetics, however the physiological mechanism by which acidosis increases oxygen cost of work is still not understood.

On the other hand, pre-exercise ingestion of 3 $mmol \cdot kg^{-1}$ BM of $NaHCO_3$, causing significant alkalosis, accompanied by a significant increase of blood lactate concentration, when compared to control study, did not affect the magnitude of the slow component of $\dot{V}O_2$ kinetics (45, 46). Moreover, lactate infusion to the working dog muscle (47) or an epinephrine induced increase of blood lactate accumulation (48, 49) was not effective to change the magnitude of the slow component of $\dot{V}O_2$ kinetics. Additionally, our previous study (46), in which the effect of pre-exercise alkalisation induced by ingestion of 3 $mmol \cdot kg^{-1}$ BM of $NaHCO_3$ on the magnitude of the slow component of $\dot{V}O_2$ kinetics was examined, has shown that the significantly reduced blood H^+ concentration and concomitantly increased blood lactate accumulation was not effective to change the magnitude of the slow component of the $\dot{V}O_2$ kinetics in humans.

In view of earlier studies, the increase of muscle H^+ may affect its efficiency in several ways including a decrease of generated force [for review see Fitts (50)]. It has been shown on animal studies that low muscle pH decreases the maximal muscle shortening velocity (51, 52). If this is the case, then the decreased muscle pH would affect the power output from the recruited muscle fibres population. Therefore, one may expect that in order to maintain the required power output, presumably more type II muscle fibres (less efficient) (18) would be recruited [for review see Sargeant, (24)]. This could be a potential cause of an increase of the slow component of $\dot{V}O_2$ kinetics observed in acidotic conditions.

Additionally, it has been shown that the enhanced muscle H^+ accumulation was accompanied by the slowing of muscle relaxation (54, 55). This would also contribute to a decrease of muscle efficiency and enhancement of the slow

component of $\dot{V}O_2$ kinetics. Another pH-dependent factor contributing to an increase of the slow component of $\dot{V}O_2$ kinetics could be the reduced free energy of ATP hydrolysis (53, 56—58).

On the other hand, it has to be remembered that most data regarding the influence of acidosis on muscle fatigue studied *in vitro* were collected during experiments performed in a rather low temperature (~24°C). A recent study by Westerblad *et al.* (59) performed on single muscle fibres preparations questions the role of H^+ accumulation in muscle fatigue. This author has shown that acidosis has only a minor effect on muscle power output, when contracting in the physiological temperature (~37°C). Moreover, recent data from Bangsbo *et al.* (60) have shown that a significant decrease of muscle pH (by about 0.2 units — from 6.82 to 6.65) did not affect the muscle efficiency expressed by the amount of ATP used per unit of work. Additionally, studies on isolated mitochondria have shown that a decrease in the extramitochondrial pH by 0.8 unit does not change the respiration rate (oxygen uptake) (25). The same result has been obtained in a theoretical simulation performed with the aid of a computer model of oxidative phosphorylation, developed by Korzeniewski & Mazat (61). In these theoretical studies a decrease in the external pH from 6.8 to 5.8 did not change the respiration rate, since the intramitochondrial pH followed the changes in the extramitochondrial pH (dropped from 7.4 to 6.4), and, as a result ΔpH (and, consequently, Δp as well as the phosphorylation potential) remained constant. Therefore, acidification *per se* does not seem to exert any significant direct effect on the efficiency of oxidative phosphorylation, but it may affect the muscle efficiency as pointed out above (51, 52, 54, 55) and in this way contribute to the slow component of $\dot{V}O_2$ kinetics.

Proton leak through the inner mitochondrial membrane

Equally, little possible seems to be the case that an increase of the proton leak through the inner mitochondrial membrane, caused by the exercise-induced increase of muscle temperature, may be the most important reason for the additional increase in the $\dot{V}O_2$: power output ratio as presented at *Fig. 1* and *2*. It has been shown that in the resting muscle the proton leak accounts for about 50% of oxygen uptake (62). An exercise induced increase of the muscle temperature could theoretically contribute to the increase in the proton leak through an inner mitochondrial membrane and to a decrease in muscle efficiency. However, during the transition from the resting state to the maximal exercise intensity, the respiration rate in the muscle increases about 20 times or more (63). Under these conditions, the contribution of the proton leak to the oxygen consumption should be less than 2.5% and therefore a possible stimulation of the proton leak by an increased temperature cannot change the $\dot{V}O_2$ significantly.

It should be mentioned, however, that some researches believe that the exercise induced rise in the muscle temperature may contribute to an increase of the proton leak through the inner mitochondrial membrane and increase the oxygen cost of high intensity cycling (25). Moreover, the most recent studies by Tonkonogi *et al.* (64) show that intensive prolonged exercise causes some increase in uncoupled muscle mitochondria respiration. According to these authors, it could contribute to the slow component of the $\dot{V}O_2$ kinetics. However, since the magnitude of the slow component of $\dot{V}O_2$ kinetics in this study was much larger that can be explained by the observed increase in uncoupled respiration, therefore the authors themselves question the significance of the uncoupled respiration in the discussed effect of the slow component of the $\dot{V}O_2$ kinetics (see, 64).

Slipping of the ATP synthase

Slipping of the ATP synthase (increase in the H^+/ATP stoichiometry) at higher phosphorylation fluxes could theoretically explain the observed decrease in the P/O ratio. Indeed, Fontaine *et al.* (65) observed an increase of energy dissipation in oxidative phosphorylation after the transition from non-phosphorylating to phosphorylating conditions. However, this effect was relatively small and did not rise with an increase of the phosphorylation flux. It has been found that almitrine, an artificial inhibitor of the ATP synthase, can induce an increase in the H^+/ATP ratio in isolated mitochondria (66). However, no factor is known which could bring about such an effect in physiological conditions. No differences in the H^+/ATP ratio have been found experimentally at different values of flux and/or Δp. Therefore, at the present stage of our knowledge, the slipping of the ATP synthase cannot account for a significant part of the decrease of the P/O ratio at maximal exercise in the skeletal muscle.

Decrease in the cytosolic phosphorylation potential

The cytosolic phosphorylation potential [ΔG_P, change in the Gibbs' free energy of ATP hydrolysis, proportional to log ([ATP]/[ADP] * [P_i]) drops in the skeletal muscle during high power output exercise for at least two reasons. Firstly, an increased ATP consumption diminishes ΔG_P *per se*. Secondly, at high exercise intensity, the oxygen concentration in muscle can drop in extreme cases to a few micromoles, what further decreases the phosphorylation potential. This is caused by the fact that a decrease in one substrate concentration (O_2) is at least partially compensated by an increase in another substrate concentration (ADP)(67). Low ΔG_P strongly stimulates the glycolytic flux, what in turn leads to lactate accumulation.

An increase in the ADP concentration (and thus a decrease in the phosphorylation potential) is necessary to stimulate the ATP production by oxidative phosphorylation and keep up with the increased ATP consumption. Nevertheless, this increase in [ADP] is rather modest, because the negative feedback via the ADP concentration, constitutes only a 'fine-tuning' mechanism responsible for adjusting the ATP supply to energy demand, while direct parallel activation of ATP production and ATP consumption by some external effector (for example calcium ions) seems to play the main role (68). The parallel activation may help to prevent a drastic decrease in the phosphorylation potential far below the level necessary for power production. Nevertheless, it has been shown that the actual phosphorylation potential in the resting muscles is only slightly higher than the minimal potential required for performing work (69), as well as that the free energy of ATP hydrolysis in the fatigued muscle may drop below that required for the optimal cell function (53, 56).

Moreover, a decrease in the cytosolic ΔG_P in the muscle cells may be a potential cause of several events leading to the increase in the $\dot{V}O_2$: power output ratio, expressed as the slow component of $\dot{V}O_2$ kinetics and as the non-linear increase in oxygen uptake at high power output exercise. It has been postulated that even a small decrease in the cytosolic free energy may affect the SR Ca^{2+} pump and prolong muscle relaxation time (70). It may lead to the rise in the resistance within contractile machinery and contribute to the drop of muscle efficiency by increasing the *internal work* in the muscle (needing some extra ATP not used for production of the external mechanical power) and thus enhancement in the $\dot{V}O_2$/power output ratio.

The above presented hypothesis that the low phosphorylation potential may be involved in the drop of muscle efficiency at high power outputs, expressed by a non-linear increase in $\dot{V}O_2$ and the slow component of $\dot{V}O_2$ kinetics, may also be supported by the fact, that the onset of the non-linearity in $\dot{V}O_2$ during incremental exercise starts at the power output at which lactate begins to accumulate. This should be recognised as an indicator of stimulation of glycolysis (chiefly via an increase in AMP and ADP concentration) as a response to a decrease in the phosphorylation potential.

THE EFFECT OF TRAINING ON THE OXYGEN COST OF HIGH INTENSITY EXERCISE

It has been reported that a few weeks period of physical training may significantly reduce the magnitude of the slow component of $\dot{V}O_2$ kinetics. Perhaps the most convincing evidence, showing a substantial decrease in the magnitude of the slow component, comes from the study by Casaburi *et al.* (34) and Womack *et al.* (17). For example, Casaburi *et al.* (34) have shown

reduction in the magnitude of the slow component of $\dot{V}O_2$ kinetics by 150—200 $ml \cdot min^{-1}$ after 8 weeks of endurance training. The decrease of the magnitude of the slow component of $\dot{V}O_2$ kinetics was positively correlated with the magnitude of the decrease in blood lactate concentration. Recently Womack *et al.* (17) were able to show a 220 $ml \cdot min^{-1}$ reduction in the slow component of $\dot{V}O_2$ kinetics as early as after two weeks of training (4 days/week). It should be mentioned that Womack *et al.* (17) postulate to exclude the changes in blood lactate accumulation, plasma epinephrine concentration and the cost of pulmonary ventilation as a potential cause of the observed training-induced decrease in the slow component of the $\dot{V}O_2$ kinetics.

CONCLUSIONS

The drop in human locomotory muscle efficiency occurring at high intensity exercise, expressed by the non-proportional increase of the pulmonary $\dot{V}O_2$:power output ratio ($\dot{V}O_2$/PO) is a well documented phenomenon. As presented above, the increased oxygen cost of work at intensity above lactate threshold has important implications for exercise performance in endurance events. Moreover, the non-proportional increase of the oxygen cost may affect the limited exercise tolerance of patients in whom the lactate threshold appears already at very low power outputs.

Understanding the physiological mechanism responsible for the appearance of the slow component of $\dot{V}O_2$ kinetics (increase in the $\dot{V}O_2$/power output ratio) requires to consider both the factors involved in *the decrease of the efficiency of the ATP-producing system*, especially mitochondrial oxidative phosphorylation (increase in the O_2/ATP ratio) and the factors involved in *the decrease of the efficiency of the contractile machinery using ATP* (increase of the ATP/power output ratio). Both of the factors may contribute to the overall effect of the non-linear increase in the $\dot{V}O_2$/PO ratio and the slow component of $\dot{V}O_2$ kinetics.

As presented in *Fig. 3*, the drop in the working locomotory muscle efficiency may be caused by effects on the ATP consumption side as well as on the ATP production side of the bioenergetic system in muscles. The decrease of the efficiency on the ATP consumption side involves recruitment of type II muscle fibres, decrease of muscle relaxation (as a result of acidification and the drop in the phosphorylation potential), hyperthermia and increase in the basal metabolic rate. The exercise induced increase in the muscle temperature may lead to *"acute transformation"* [see Sargeant, (24)] of type I muscle fibres towards their faster properties, such that they are no longer operating at and around their optimum velocity for the maximum mechanical efficiency, as recently suggested by Ferguson *et al.* (32). In order to maintain the required

power output, the resulting drop in ΔG_P will accelerate glycolysis and mitochondrial respiration in the working locomotory muscle causing a need for the "additional" oxygen uptake. Additionally, intensification of the hyperventilation due to the developed acidosis and recruitment of the posture stabilising skeletal muscles will contribute to the "non-proportional" pulmonary oxygen uptake occurring above the CP-$\dot{V}O_2$.

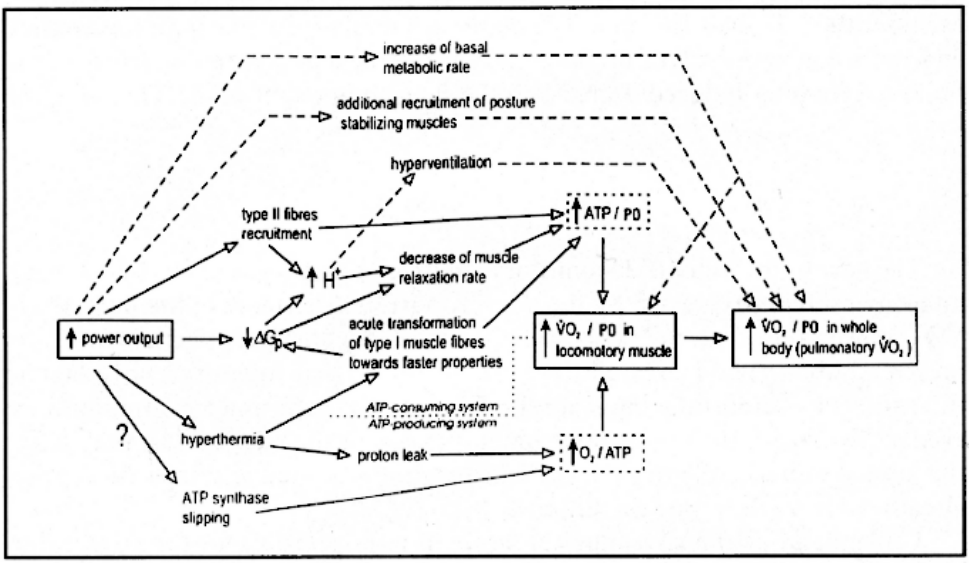

Fig. 3. Possible factors involved in the mechanism responsible for the decrease of the oxygen uptake to power output ratio ($\dot{V}O_2$/PO) at high intensity exercise.

On the side of the ATP production, a small effect on the decrease of muscle efficiency may be caused by an increase of the proton leak. One could also consider a theoretically possible, but having only a weak experimental basis, the slipping of the ATP synthase (and/or the ATP carrier as well as the phosphate carrier).

As presented above, in the physiological background of the non-proportional increase of the oxygen cost at high power outputs, expressed by the slow component of $\dot{V}O_2$ kinetics (4) and by the change point in $\dot{V}O_2$ (6, 9, 71), a large number of factors may be involved (*Fig. 3*). Despite the fact that the precise physiological mechanism responsible for this effect remains to be established, it is obvious that the non-linear increase in the oxygen uptake occurring above the CP-$\dot{V}O_2$ decreases influence the human muscle power generating capabilities, its mechanical efficiency and exercise tolerance. Therefore understanding of the physiological background of this phenomena belongs to the priority of research in human physiology (for review see eg. 4, 9, 10, 12).

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