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18. Muscle fatigue following prolonged dynamic exercise

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Abstract. Muscle fatigue defined as the reduction in the maximum force that a muscle can exert, may develop during prolonged dynamic exercise such as running and cycling. Reduction in maximal voluntary contraction (MVC) force appears generally greater after prolonged running than cycling and can reach ~40% at the termination of exercise. Central fatigue i.e. reduction in efferent motor command to the active muscles has been evidenced after prolonged exercise with different techniques such EMG, electrical stimulation or transcranial magnetic stimulation. The reduced neural drive may be due to spinal and supraspinal mechanisms, and occurs especially in the latter stage of the exercise. Changes at peripheral level such as failure of the action potential transmission, excitation-contraction coupling or cross bridge cycling have also been identified as a possible cause of fatigue during long-duration exercise. The contribution of peripheral and central factors to the decline in muscle strength and the time course of the impairment during prolonged exercise are examined in this chapter.

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Introduction

In recent years, there has been considerable interest in the performance of prolonged whole-body exercise, especially cyclic activities, such as running, cycling, or cross-country skiing. Among the multiple physiological alterations specific to long-duration exercise, there has been increasing research on exercise-induced muscle fatigue [e.g. 1]. Fatigue is an ongoing process that occurs even under conditions where performance is maintained at a constant level, and that transforms progressively the functional state, with exhaustion being the point at which exercise is terminated. The degree of muscle fatigue can be estimated by quantifying the reduction in maximal voluntary contraction (MVC) force induced by exercise. Fatigue can originate from several potential sites classified as proximal (central fatigue) and distal (peripheral fatigue) to the neuromuscular junction, respectively [2].

Long-duration exercise (from 30 min to several hours) differs from short-intense exercise by the energy contribution from glycolytic precursors and the anaerobic component which is of lower relative importance in the former exercise. The intensity and the duration of the exercise may thus influence muscle metabolism such as the kinetics of the glycogen depletion. Fatigue during short-intense exercise is frequently associated with accumulation of metabolic products, while fatigue during prolonged exercise is often linked to non-metabolic mechanisms such as depletion of energy substrates, especially carbohydrates. Biochemical and structural changes in muscle might also affect neuromuscular function during prolonged exercise. It has also been shown that specific physiological changes occur during long-duration exercise including increased plasma ratio of free tryptophan/BCAA (Branched-Chain Amino Acid) and increased blood levels of free fatty acids, free tryptophan, and brain serotonin [3]. These systemic alterations are suspected to alter the drive from central nervous system to the working muscles.

Because the physiological responses depend on both intensity and duration of the exercise, the mechanisms that limit performance are different between short- and long-duration exercises. In addition to peripheral fatigue caused by metabolic changes and/or muscle damage in the muscle, central fatigue, i.e. the reduction in efferent motor command to the active muscles, can also impair neuromuscular function during prolonged exercise. Nevertheless, the relative contribution of peripheral and central mechanisms to the decrease in force generating capacity and thus to the decline in performance during long-duration exercise remains unclear. Therefore, the purpose of this chapter is to examine the central and peripheral mechanisms contributing to muscle fatigue occurring during prolonged whole-body

exercise. The vast majority of the studies cited in this chapter refer to exercises longer than 30 minutes, with some minor exceptions.

1. Reduction in maximal strength capacity following prolonged exercise

It is possible to examine muscle fatigue during and following prolonged exercise by performing static contractions during short interruptions or at the completion of exercise. Because the knee extensor muscles are involved in all whole-body exercises and the knee extension force measurement is relatively easy, MVC force of the knee extensor muscles has been fully investigated following different kinds of prolonged exercise performed in laboratory or in race conditions (Table 1). For these muscles, the strength loss after long- duration exercise ranged from 8 to 41%, depending on duration, intensity

Table 1. Decrease in isometric maximal voluntary contraction (MVC) strength in the knee extensor muscles after different prolonged running, cycling and cross-country (X-C) skiing exercises.

References	Exercise	Time	Intensity/ Distance	MVC loss (%)
Davies & Thompson (4)	Running - L	240 min	65%VO_2max	25
Nicol et al. (5)	Running - R		42 km	26 ± 14
Lepers et al. (6)	Running - L	120 min	28 km	19 ± 9
Millet et al. (7)	Running - R	511 min	65 km	30 ± 18
Millet et al. (8)	Running - R	188 min	30 km	24 ± 15
Place et al. (9)	Running - L	300 min	52 km-55%VO_2max	28 ± 27
Gauche et al. (10)	Running - R	413 min	55 km	37 ± 3
Petersen et al. (11)	Running - R	154 min	42 km	23 ± 7
Millet et al. (12)	Running - L	1119 min	149 km	41 ± 17
Sahlin & Seger (13)	Cycling - L	85 min	75%VO_2max *	34 ± 13
Booth et al. (14)	Cycling - L	72 min	75%VO_2max *	28 ± 3
Bentley et al. (15)	Cycling - L	30 min	80%VO2max	13
Lepers et al. (16)	Cycling - L	120 min	70%VO_2max	13
Lepers et al. (17)	Cycling - L	30 min	80%VO_2max	13 ± 8
Lepers et al. (18)	Cycling - L	300 min	55%VO_2max	18 ± 12
Millet et al. (19)	Cycling - R	280 min	140 km	9
Sandiford et al. (20)	Cycling - L	90 min	50%VO_2max	21
Leppik et al. (21)	Cycling - L	72 min	74%VO_2max*	26
Sarre et al. (22)	Cycling - L	60 min	65%VO_2max	14 ± 12
Vallier et al. (23)	Cycling - L	180 min	60%VO_2max	16 ± 10
Presland et al. (24)	Cycling - L	69 min	70%VO_2max *	29 ± 11
Lepers et al. (25)	Cycling - L	30 min	75% VO_2max	11 ± 6
Theurel & Lepers (26)	Cycling - L	30 min	Variable	12
Del Coso et al. (27)	Cycling - L	120 min	63% VO_2max	11 ± 5
Marcora et al. (28)	Cycling - L	14.5 min	86%VO_2max *	16
Viitasalo et al. (29)	X-C skiing - R	330 min	85 km $^{\$}$	10
Millet et al. (30)	X-C skiing - R	160 min	42 km	8

* Exercise performed until exhaustion , $^{\$}$Strength losses measured 1-2 h after the race was finished. R: race condition, L : laboratory condition. Mean ± SD

(i.e. % VO_2max) and type of exercise performed (e.g. running, cycling or cross-country skiing) [4-30]. Since the MVC measurements are usually performed one or two minutes after the termination of the exercise, the real strength loss immediately after exercise remains unknown because recovery processes inevitably already take place during this short time.

For running, the greatest MVC losses were observed after long-distance events with a substantial vertical gradient and after ultra endurance exercise. Gauche et al. [10] found a knee extensors MVC reduction of 37% after a 55 km running race including a 6000 m vertical gradient (3000 m up and 3000 m down). Millet et al. [12] reported a 41% MVC loss after an ultra endurance running exercise where trained subjects performed ~150 km on a treadmill with no gradient. Strangely and in contrast to cycling, no data are available for running exercise performed until exhaustion. The decrease in MVC force following running seems to depend on exercise duration and whatever the duration or the intensity of the exercise MVC loss seems limited to values close to 40% (see Figure 1).

For cycling, the greatest MVC force losses were observed when the exercise was performed until exhaustion (Table 1). Interestingly, the strength loss appears generally smaller after cycling compared to running exercise of similar duration and intensity. For example, MVC force decreased by 16% after 180 min cycling [23], while it reached 24% following the same running exercise duration [8]. Similarly, a 300 min cycling exercise induced a strength loss of 18% [18], while a running exercise of the same duration and intensity (55% of maximal oxygen uptake - VO_2max) reduced MVC force by

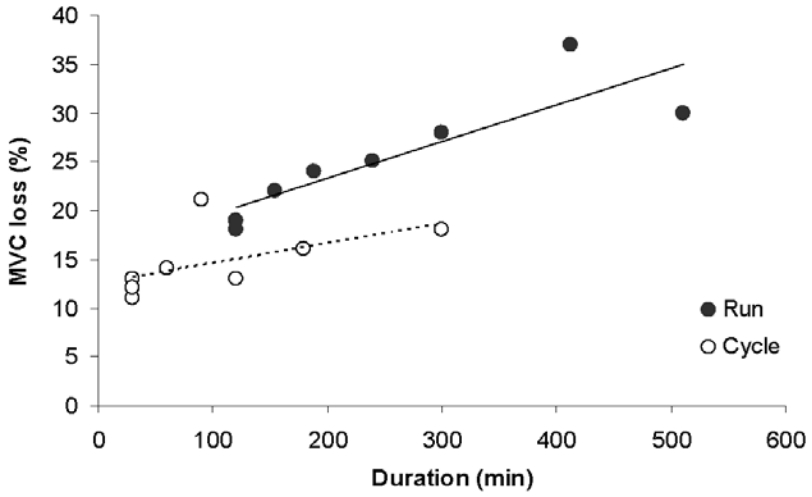

Figure 1. Relation between the maximal voluntary contraction (MVC) loss of the knee extensor muscles and the exercise duration for running [4, 6, 7, 8, 9, 10, 11] and cycling [15-18, 20, 22, 23, 25-27] exercises.

28% [9]. In contrast to running, no data are available on cycling exercise for a duration longer than 5-h, while it is very common in the field of cycling events. The lower strength loss in the knee extensor muscles observed following cycling compared to running is probably related to the type of contraction. For a stretch shortening cycle exercise like running, prolonged exercise especially with negative gradient may contribute to a greater active strain in knee extensor muscles, thereby leading to a greater amount of muscle and connective tissue damage [31].

Some studies have examined the effect of cycling cadence on knee extensors strength reduction. Lepers et al. [17] found that the MVC loss, ranging from 9 to 13%, appeared independent of the pedaling rate throughout a range of cadences habitually adopted by cyclists (from 69 to 103 rpm) during a 30 min endurance cycling exercise. Sarre et al. [22] examined muscle fatigue after a longer cycling exercise consisting in 60 min performed at an intensity corresponding to 65% of the maximal aerobic power output (MAP) i.e. the power output at VO_2max, for a larger range of cadence (from 50 to 110 rpm). The results revealed a non-statistically significant trend for the knee extensors MVC to decrease to a larger extent at 110 rpm (-18%) compared to 50 rpm (-11%) and freely chosen cadence (-14%). Although unexpected, it is interesting to note that compared to lower or greater cadences, the freely chosen cadence induce similar fatigue on knee extensors' strength capacities. Further studies are required to examine the interaction between fatigue and cadence for cycling exercise performed for longer durations or at higher intensities.

The effects of variable versus constant intensity on muscle fatigue during prolonged exercise have been examined for cycling. Lepers et al. [25] recently demonstrated that varying power output with alternating ± 15%, ± 5%, and ± 10% of 75% MAP (i.e. 86.25%, 63.75%, 78.75%, 71.25%, 67.50%, and 82.50% MAP respectively) approximately every 5 min during 30 min induced similar alterations of maximal knee extensors strength capacity compared to those observed after constant power output cycling. In contrast, a protocol with alternating high power output periods (200, 150 and 100% of MAP during 10, 15 and 20 s, respectively) induce greater reductions in MVC torque than a constant intensity protocol [26]. These results support the hypothesis that large variations in exercise intensity, including efforts beyond the MAP, exacerbated neuromuscular fatigue. However, these findings need to be confirmed for running.

Few studies have focused on muscles other than the knee extensors. For the plantar flexor and dorsiflexor muscles, MVC force losses after prolonged running ranged from 9 to 30% (See Table 2) [11,12, 32-35]. After marathon running in laboratory settings, Avela et al. [33] found a 30% reduction in plantar

Table 2. Decrease in isometric maximal voluntary isometric contraction (MVC) strength in plantar flexor and dorsiflexor muscles after different prolonged running.

References	Exercise	Time	Intensity/ Distance	MVC loss (%)
Plantar Flexors				
Davies & White (32)	Running - L	60 min	80% VO_2max	9
Avela et al. (33)	Running - L		42 km	30 ± 11
Saldanha et al. (34)	Running - L	120 min	27 km- 75%VO_2max	17 ± 16
Petersen et al. (11)	Running - R	154 min	42 km	18 ± 8
Millet et al. (12)	Running - L	1119 min	149 km	30 ± 13
Dorsiflexors				
Ross et al. (35)	Running - L	208 min	42 km	18 ± 7

flexors MVC while Petersen et al. [11] reported only a 17% reduction in MVC force on the same muscular group after a marathon race. Recent observations from Millet et al. [12] showed that plantar flexors MVC force decreased by 30% following an ultra endurance running exercise (~ 150 km). It appears that even if the anatomical and functional properties of knee extensor and plantar flexor muscles differ, their maximal strength capacities following prolonged exercise are reduced to a similar extent.

For reasons of technical simplicity, MVC is usually evaluated in isometric conditions; however the type of muscular contraction performed during the evaluation of the MVC (isometric vs. concentric vs. eccentric) influences the reduction in strength. Indeed, under concentric conditions the strength loss of the knee extensor muscles appears generally lower than the isometric counterpart. For example, the MVC loss was greater under isometric (19%) and eccentric contractions (18-21%) than under concentric ones (11-14%) after running for 2 h [6]. Similar results were observed for cycling since MVC decrease after 5-h cycling was 18% and 9% for isometric and concentric contractions, respectively [18]. Although reductions in eccentric strength capacity after prolonged exercise have been less investigated, eccentric losses tended to be similar after cycling [16] and greater after running [6] in comparison with concentric losses. Whatever the type of exercise performed, force reduction of the knee extensor muscles appears to be dependent of the modes of contraction evaluated, but the reasons of this finding remain unclear. Moreover, it is not known if muscle fatigue following prolonged exercise depends on muscle length (i.e. the angle of testing), but previous studies suggested that there are length-dependent effects of fatigue on maximum force production [36].

It is well established that long-duration exercise reduces the maximal voluntary force-generating capacity. Nevertheless, for exercise prolonged several hours the timing of alterations is still poorly understood. In a study examining the knee extensors MVC after each hour during a 5-h cycling exercise, Lepers et al. [18] found that the decrease of the maximal strength capacity is more pronounced in the second part of the exercise, i.e. after the third hour (16-18%) compared to the first three hours (8-10%). Similar results were found during a 5-h running exercise, where MVC decreased by 8 to 14% in the first three hours, while MVC reduction reached 26-28% in the last two hours [9]. These observations suggest that MVC force does not decrease linearly during a 5-h prolonged exercise but seems to be amplified after the third hour.

2. Central fatigue

2.1. Changes in EMG activity during prolonged exercise

Central fatigue defined as a reduction in efferent motor command to the active muscles [2] can be assessed by electromyography (EMG) activity. For example, surface EMG can be used during long-duration exercise to examine the changes in the activity level of working muscles. During prolonged cycling at the constant power output, the EMG activity of the lower limb muscles has been found to either remain stable or increase depending on the studied muscles and the pedaling rate [22, 37-39]. For example, during a 30 min cycling time-trial at self-selected work intensity, Duc et al [38] found that the EMG activity of the *Vastus Medialis* and *Rectus Femoris* muscles remained constant while the EMG activity of the two knee flexor muscles (*Biceps Femoris a*nd *Gastrocnemius*) tended to increase with time. EMG activity of *Vastus Lateralis* and *Rectus Femoris* muscles significantly increased only during 1-h of cycling exercise performed at 110 rpm but not at the freely-chosen cadence [22]. Because the timing of onset and offset of muscle bursts was not altered by fatigue throughout the prolonged exercise, these last authors suggested that the timing of activation set by the central nervous system in order to provide the power output required by the exercise is held constant throughout the exercise, but that quantitative aspects of the central drive such as EMG activity are increased in order to adapt to the progressive occurrence of fatigue.

However, the typical increase in EMG did not exceed 10% during cycling exercise. For example, Takaishi et al. [37] found an increase of the integrated EMG (iEMG) of the *Vastus Lateralis* muscle close to 10% during a 15-min cycling exercise at 85% VO_2max. Similarly, Vercruyssen et al. [39]

found a small (~ 8%) but significant increase in the *Vastus Lateralis* muscle iEMG after 1-h cycling at an intensity corresponding to 75% of the maximal heart rate. Increases in EMG indicate an increased recruitment and/or discharge rate of active motor units and/or increased motor units synchronization. It seems that with fatigue, more neural input to active muscles is required to produce the same power output therefore indicating a reduction of neuromuscular efficiency. Nevertheless, it should be mentioned that these observations were made for exercise not exceeding one hour. The increase in neural input to muscles needs to be verified for exercises performed at lower constant intensities exceeding one hour.

Very few studies examined EMG activity of leg muscles during prolonged running exercises. Place et al [9] did not find any alteration of *Vastus Lateralis* and *Rectus Femoris* muscles EMG activity during 5-h of running at 55% of the maximal aerobic velocity. In contrast, Hausswirth et al [40] showed a ~ 22% increase in the *Vastus Lateralis* iEMG during the last 45 min of a marathon. The discrepancy between these two studies may be due to the different exercise intensities and durations. During submaximal running, muscle contractions could be performed by only a portion of the motor unit pool. A change in activity between different motor units might occur with fatigue and could contribute to the stability of EMG activity during prolonged exercise performed at low to medium intensities.

In contrast, when maximal efforts such as sprints are performed occasionally during a prolonged exercise, EMG results differ from a constant intensity exercise. St Clair Gibson et al. [41] found that iEMG activity of the *Rectus Femoris* muscle fell parallel with reduction in power output during bouts of high-intensity exercise performed during a 100-km cycling time trial (≈ 150 min). These data corroborate the observations of Lepers et al. [18] who showed that the MVC reduction evaluated by short interruptions during a 5-h cycling exercise was associated with a decrease in the EMG activity of the vastii muscles. Moreover, the EMG reduction was more pronounced in the *Vastus Medialis* muscle suggesting that prolonged cycling may differently affect activation of synergist muscles. Consequently, in conjunction with the development of fatigue, an alteration in the coordination pattern of the cycling movement within the synergist muscles is probable in order to furnish the adequate power output. Further studies examining muscular activity of synergist muscles during long-duration cyclic activity such as cycling or running are needed to better understand the changes in recruitment pattern observed with fatigue. However, EMG is a global index measured at the muscular level that can be influenced by peripheral and central changes.

2.2. Changes in neural drive following prolonged exercise

Central fatigue could also be evidenced by a progressive exercise-induced reduction in voluntary activation or neural drive to the muscle, resulting in a decline in maximal force production. One technique to quantify a central activation failure consists of analyzing the changes in the maximal EMG activity (iEMG or Root Mean Square, RMS) during a MVC while taking into account of the changes in the maximal compound motor unit action potential (M-wave). Indeed, a decrease in maximal EMG activity can be due to a reduction in central drive to the muscles but also to a reduction in the neuromuscular transmission-propagation i.e. sarcolemmal excitability. Thus reductions in the EMG activity without examining changes in M-wave characteristics can not be interpreted as a decrease of the efferent motor command to the muscles. Therefore, when maximal EMG is used to evaluate central activation, this value needs to be normalized to the maximal M-wave for the considered muscle, such as amplitude or RMS (RMS_M), by using for example the RMS_{MVC}/RMS_M ratio. A reduction in the MVC RMS without a reduction in RMS of the M-wave, i.e. a decrease in RMS_{MVC}/RMS_M ratio, could be interpreted as central activation failure.

Previous studies found a decrease in maximal EMG activity close to 40% during MVC of the knee extensor muscles at the end of long-duration exercise [e.g. 5]. However, these high decreases in maximal EMG could also be due to the presence of lower sarcolemma excitability, as maximal EMG was normalized by the M-wave, in addition to the reduced neural command in fatigued state. Data from more recent studies, taking into account the changes in excitability, found that for the *Vastus Lateralis* muscle the decrease in RMS_{MVC}/RMS_M ratio could be variable (from 10 to 45%) following long-duration exercise (see Figure 2). This great variability suggests that the measurement of maximal EMG even normalized by the M-wave, can not alone well characterize central fatigue. Millet et al. [30] even found that after a X-country ski marathon the amplitude of M-wave and the MVC RMS of the *Vastus Lateralis* muscle decreased with fatigue to a similar extent, so that the RMS_{MVC}/RMS_M ratio was unchanged.

Studies usually focus on the effects of fatigue on agonist muscles however little information is available on antagonist muscles. It has been shown that during progressive fatigue of knee extensor muscles in isometric conditions, antagonist activation increases and contributes to the loss of extensor force-producing capacity. However, it is not known whether coactivation is higher in fatigued state following prolonged exercises and this hypothesis requires testing in the future.

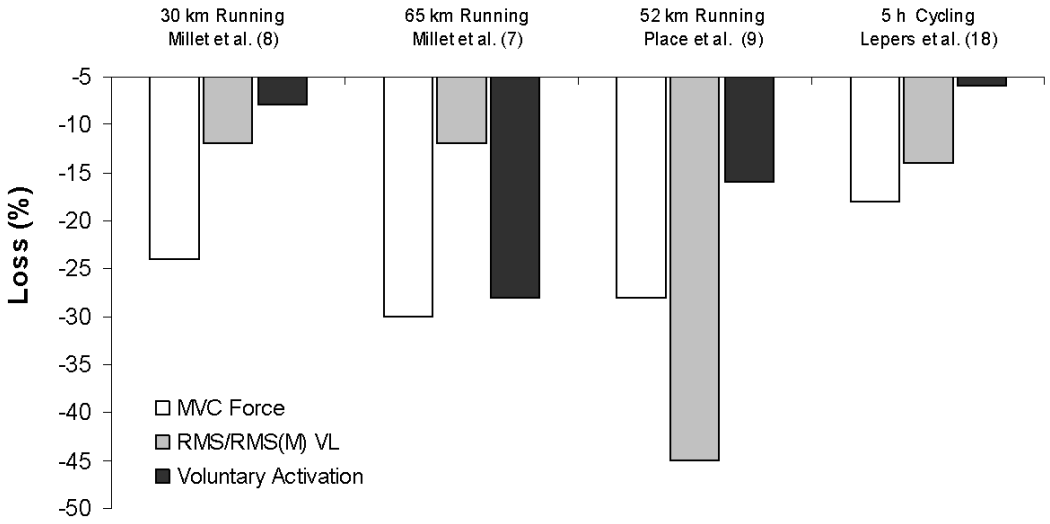

Figure 2. Reduction in maximal isometric voluntary contraction (MVC) force of the knee extensor muscles, RMS/RMS(M-wave) ratio of the *Vastus Lateralis* muscle (VL), and voluntary activation assessed during MVC following different prolonged exercises.

Even though surface EMG is extensively used during and following dynamic exercise to examine the alteration of muscle activation, EMG results must nevertheless be considered with caution since cancellation or synchronization of motor unit action potential phenomena may also occur [42]. Surface EMG is an easy way to assess the changes in activation of different synergist muscles of the same muscle group such as quadriceps muscle. However, surface EMG does not give information about deeper muscles such as the *Vastus Intermedialis* for example that is also involved in knee extension. For that reason, the measurement of the central activation by the technique of transcutaneous nerve stimulation may represent a more global approach of changes in neural drive to the muscles.

2.3. Reduction in voluntary activation

The use of transcutaneous electrical and magnetic stimulation of a peripheral motor nerve to interpolate a twitch or several stimuli on a MVC is frequently used to detect an inability of the central nervous system to maximally drive motor units in the working muscle. If the superimposed stimulation during the MVC produces a twitch-like increment in the force from the contracting muscles, voluntary activation is less than 100%. Voluntary activation can be derived using the expression: (1 – superimposed twitch/resting twitch) × 100 [2], where superimposed twitch is the size of the

interpolated twitch and resting twitch is the size of a control twitch produced by identical nerve stimulation in a relaxed (potentiated or not) muscle. A decrease in voluntary activation level may be interpreted as a sign of central fatigue even if recent data in animal studies challenged this idea [43]. Determination of the voluntary activation by the twitch interpolation method requires several trials to give accurate and reliable values. Unfortunately, multiples measurements are not always possible during a long lasting fatigue protocol and this could limit the accuracy of the data. However, using this so-called twitch interpolated technique, it has been deduced that central fatigue contributed to the force loss experienced following prolonged whole-body exercise.

Figure 3 synthesizes the results concerning the relation between average MVC loss and maximal voluntary activation level reduction after different prolonged exercises. In general, voluntary activation loss was lower than MVC loss attesting that central fatigue could not explain totally the reduction in strength capacity induced by exercise. It should be mentioned that most of the time; authors reported a great inter-individual variability in voluntary activation loss following exercise that limits the twitch interpolation method in the assessment of central fatigue. Methodological issues in the use of the interpolated twitch technique have been recently investigated by Folland and Williams [44].

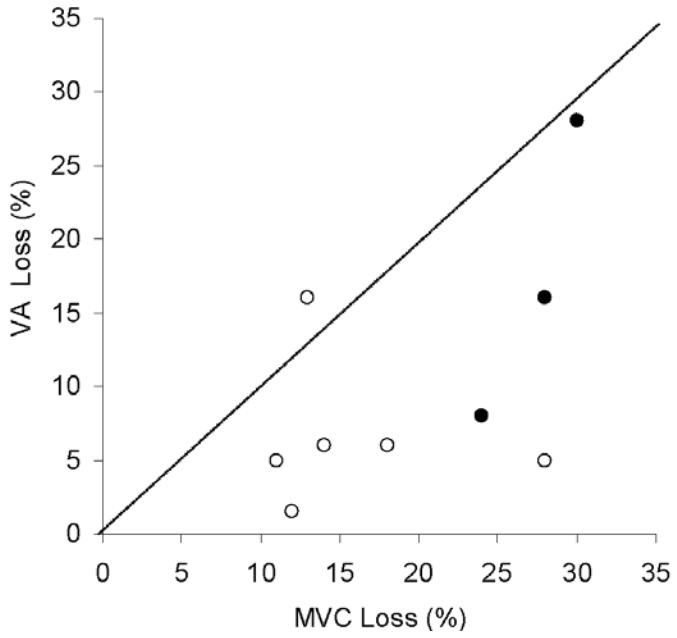

Figure 3. Reductions in maximal voluntary contraction (MVC) and maximal voluntary activation (VA) assessed during the MVC following different prolonged exercises. Doted line represents the identity line. Black circle: running exercise [7, 8, 9], White circle: cycling exercise [15,17, 18, 22, 26, 27].

There is lot of evidence that central fatigue contributes substantially to the reduction of MVC force observed following prolonged exercise. Nevertheless, the timing course of central fatigue during prolonged exercise remains poorly understood. Data from 5h-running experiment [9] (Figure 4A) tended to show that central activation failure occurred especially in the latter stage of the exercise and thus the decrease of muscle strength in the early stage of prolonged exercise might therefore be due primary to peripheral mechanisms. In contrast, data from 5h-cycling experiment [18] indicated an immediate drop of activation level that stayed constant over the time (Figure 4B).

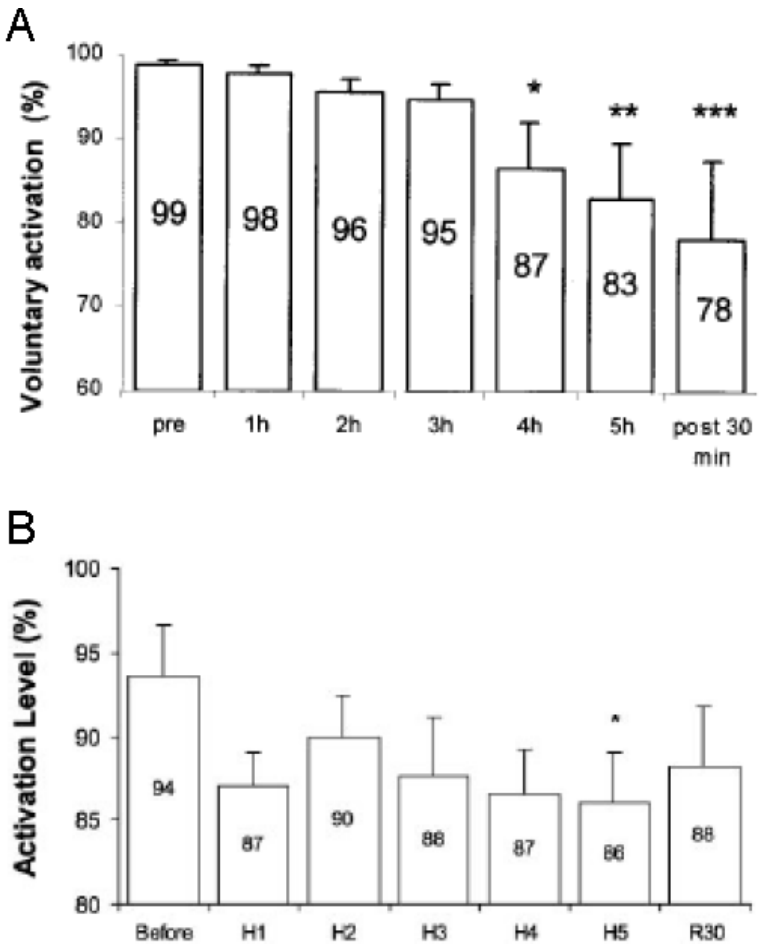

Figure 4. Voluntary activation estimated by the superimposed method before (pre), during (1 h, H1: 60th min; 2 h, H2: 120th min; 3 h; H3: 180th min; 4 h, H4: 240th min; immediately after (5 h, H5: 300th min); and 30 min after (R30) a 5-h running (A) and a 5-h cycling (B) exercise. *P < 0.05; **P < 0.01; ***P < 0.001: Statistically significant compared with preexercise values. From Place et al. [9] and Lepers et al. [18].

2.4. Spinal and supraspinal fatigue

The reduced neural drive to the motoneurons may be due to spinal and/or supraspinal alterations. Fatigue can occur at levels upstream of corticospinal neurons, presumably due to neurotransmitter changes, which could result in an impaired efficiency in generating the central command. Central fatigue could also occur at the spinal level from peripheral reflex inhibition of the α-motoneurons pool and/or disfacilitation of the α-motoneurons by muscle spindle afferents.

Avela et al [33] showed that running a marathon induced an initial decline in plantar flexor muscle function and reflex sensitivity and a delayed second decline in the reflex parameters associated with lengthening action of the muscle. These authors suggested that the initial decline in neural input to the muscle is of reflex origin in the fatigued muscle. The results of passive reflex measurements implied the possibility of fatigue, whether metabolic or mechanical in nature, in the intrafusal fibers themselves. However, the delayed second decline in some of the reflex parameters might be attributable to secondary injury (inflammation response), which might well point to the involvement of the group III and IV muscle afferents. Indeed, peripheral inhibitory input is thought to be conveyed from receptors sensitive to metabolic changes in exercising muscles via small diameter III/IV afferents [45]. Thus, fatigue induced by prolonged exercise may influence the excitation-inhibition balance of motoneurons.

Supraspinal fatigue is a component of central fatigue that can be defined as suboptimal output from the motor cortex [2]. A decrease in voluntary activation estimated by the superimposed twitch suggests that less stimulated axons are voluntarily recruited and/or are discharging at lower rate. However, voluntary activation can also be measured with transcranial magnetic stimulation (TMS) and reveals some different results. If a superimposed twitch is evoked during a MVC by cortical stimulation then it is implied that the output from the motor cortex is not optimal to drive the muscle maximally. Failure of voluntary drive at or above the level of motor cortical output contributes to the manifestations of fatigue [35].

One recent study investigated the changes in corticomotor excitability following a prolonged dynamic exercise [35]. The authors measured the isometric ankle dorsiflexion force and the EMG responses of the *Tibialis Anterior* in response to magnetic stimulation of the peroneal nerve and the motor cortex after running a marathon. The decrease in both motor evoked potential amplitude and voluntary activation, assessed by twitch interpolation via TMS demonstrated central fatigue, of supraspinal origin, indicating that suboptimal output from the motor cortex occurs following marathon running.

Nybo et al. [46] recently addressed mechanisms of importance for hyperthermia-induced fatigue during short intense activities and prolonged exercise in the heat. Prolonged exercise may induce homeostatic disturbances within the central nervous system that subsequently attenuates motor activation. Central fatigue appears to be influenced by neurotransmitter activity of the dopaminergic system, but may primarily relate to inhibitory signals from the hypothalamus arising secondary to an increase in brain temperature [46].

In conclusion, the precise neural mechanisms either spinal or supraspinal involved in central fatigue during long-duration exercise are not yet elucidated. Further investigation combining techniques exploring supraspinal component (such as TMS) with techniques examining the spinal level with reflexology could help to better understand the mechanisms of central fatigue during prolonged exercise.

3. Peripheral fatigue

Peripheral fatigue can be defined as a decrease in the force-generating capacity of the skeletal muscle owing to processes occurring at, or distal to, the neuromuscular junction. These could include failure or disruption of the action potential transmission, excitation-contraction coupling or cross-bridge cycling in the presence of unchanged or increasing neural drive [47].

Peripheral fatigue underlying the neuromuscular mechanisms, such as excitation-contraction coupling process, can be investigated by studying the contractile and electromyographic responses to motor nerve stimulation without any voluntary contraction i.e. muscle at rest. For the knee extensor muscles, percutaneous electrical or magnetic stimulation is generally applied to the femoral nerve by using a monopolar cathodal electrode pressed in the femoral triangle. For plantar flexor muscles, the posterior tibial nerve is stimulated with the cathodal electrode pressed in the poplitea fossa. When a single stimulation is applied, it is therefore possible to record the mechanical response (twitch) using an isometric ergometer and the electromyographic response corresponding to the compound muscle action potential (M-wave) with surface EMG. All the motor units are considered to be recruited when an increase in current intensity do not induce a further increase in twitch amplitude and in the peak-to-peak amplitude of the M-wave. The most common parameter analyzed from the mechanical response of the evoked twitch is the peak twitch tension i.e. the highest value of twitch tension production. Others parameters can be also analyzed such as twitch contraction time, i.e., the time from the origin of the mechanical response to peak twitch; half-relaxation time, i.e., the time to obtain half of the decline in

twitch maximal torque, maximal rate of twitch torque development, i.e., maximal value of the first derivative of the torque signal; and maximal rate of twitch torque relaxation, i.e., the most negative value of the first derivative of the torque signal. In practical terms, potentiated twitch should be preferred because it has been suggested that potentiated twitch force (i.e. following a MVC) was a more sensitive measure of fatigue than unpotentiated twitch force [48]. From the M-wave, peak-to-peak amplitude, peak-to-peak duration and root mean square (RMS) of the M wave can be analyzed. The change in M-wave duration is an index of neuromuscular propagation impairment [49]. Since peak to peak amplitude and duration can change in different manner, M-wave RMS represents a better quantification of muscle excitability.

3.1. Changes in neuromuscular propagation

Changes in M-wave parameters could represent both a failure in the neuromuscular transmission and/or a reduction in the ability to propagate action potentials [50]. However, M-wave characteristics can be affected by the synchronization of muscle fiber action potentials or the degree of dispersion in the release of transmitter from motor nerve terminals. According to some authors, changes of M-wave characteristics do not reflect modifications of intracellular action potential [51]. During prolonged exercises, muscular edema and sweat can complicate interpretation of the EMG signal [52]. Therefore, changes in M-wave following prolonged exercises need to be interpreted with caution.

There is a lot of discrepancy in the changes in M-wave parameters after prolonged exercise and the M-wave is not always significantly altered by prolonged exercises (see table II, from Millet & Lepers [1]). Also, there were large differences in the M-wave alterations between subjects after exercise. When significant changes were observed, there were (i) a decrease in peak-to-peak amplitude or RMS of the M-wave and (ii) an increase of peak-to-peak duration. In general, M-wave duration is much less altered than amplitude or RMS values, suggesting a reduction in the action potential transmission rather than a propagation failure. The lower muscle fiber excitability could originate from changes in blood metabolites concentration such an elevated blood ammonia concentration [53]. A reduced chemical gradient for Na^+ and K^+ across the sarcolemma is another hypothesis frequently proposed. Plasmatic $[K^+]$ increases after long duration exercises [50, 54]. Since the rise in $[K^+]$ in the interstitium surrounding the fibers may be larger than in the blood, the muscle fibers undergo a more pronounced reduction in chemical gradient than estimated from the plasmatic $[K^+]$. The consequence is an alteration of sarcolemmal excitability or tubular system excitability so that large alterations

of sarcolemmal excitability were anticipated after prolonged exercise. However, the absence or the moderate changes of M-wave characteristics following prolonged exercise suggest that sarcolemmal excitability does not play a fundamental role in fatigue for such exercise [33].

3.2. Changes in twitch mechanical response

Changes in peak twitch tension for the knee extensors muscles following different prolonged exercises are summarized in figure 5. Peak twitch force is reduced after cycling and very often potentiated after running exercises. Only one study reported a reduction of peak twitch after a prolonged running exercise corresponding to a 3-h running event. Peak twitch potentiation has also been reported after a ski-skating marathon (+ 7%; [30]).

The precise mechanism for the decrease in peak twitch tension following prolonged cycling is not known and several processes might be impaired, including a reduced Ca^{2+} release from sarcoplasmic reticulum and, reduced capacity of cross bridges to form strong bonds. These alterations in turn may be due to metabolic changes induced by exercise such as inorganic phosphate accumulation. In contrast to cycling, peak twitch potentiation has been found after prolonged running exercises for knee extensor and plantar flexor muscles [7], suggesting that stretch-shortening cycle may also play a role in twitch potentiation observed following running. Knowing that stiffness of the series elastic component may be altered with fatigue [55, 56], this could influence the evoked twitch mechanical response. Based on animal studies, it is now assumed that potentiation is due to regulatory myosin light chain phosphorylation [57]. Phosphate incorporation is known to increase rate of force development and Ca^{2+} sensitivity; this could be an explanation for the higher peak twitch and for the tendency to the greater maximal rate of twitch tension development observed in some studies.

It is well reported that long-distance running leads to damage of muscle fibres, especially since running involves a component of eccentric work [58, 59]. Total muscle Ca^{2+} and plasma creatine kinase increase after prolonged running of up to 100 km duration [58], and it has been suggested that Ca^{2+} accumulation in the muscle may contribute to post exercise muscle damage. The changes in the peripherally evoked twitch force after prolonged running may be due to such disruptions in the muscle contractile machinery. The coexistence of potentiation and fatigue of a single twitch makes it difficult to quantify either process independently [60] and could explain the large diversity of these results. Recent data suggest that potentiated twitch (i.e. after a MVC) may be a better index to estimate the effect of fatigue on excitation-contraction coupling [48].

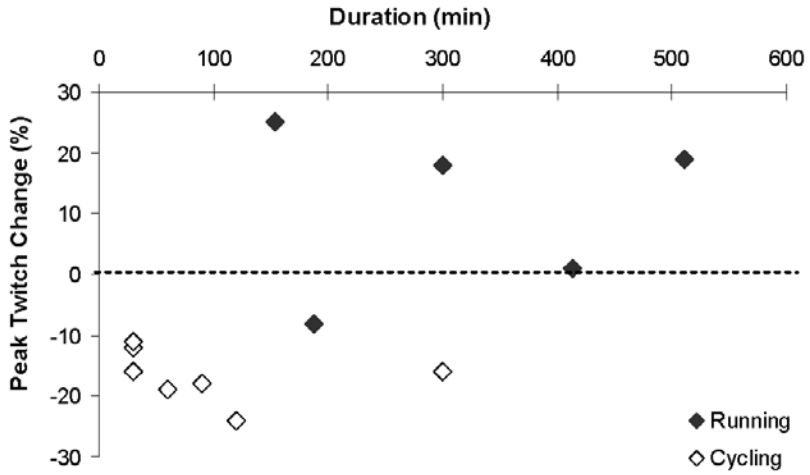

Figure 5. Changes in evoked peak twitch tension of the knee extensor muscles following running [7, 8, 9, 10, 11] and cycling [16-18, 20, 22, 25, 26] exercises of different durations.

Moreover, changes in excitation-contraction coupling may depend on the specific muscles investigated. In contrast to previous results on knee extensor muscles, Ross et al [35] found for the *Tibialis Anterior* muscle that following marathon running, there was no change in M-wave amplitude, but a decrease in resting potentiated twitch torque. These results suggested that disruption of the structure of the *Tibialis Anterior* muscle fibre and the excitation-contraction coupling mechanism were the likely cause of this peripheral fatigue, rather than any reduction in action potential transmission.

The above results showed that peak twitch may be influenced by many parameters, and therefore can not be used to investigate peripheral muscle fatigue. Moreover, during a single twitch the activation of contractile protein is not maximal, thus multiple stimuli are necessary to explore the muscular contractile properties.

3.3. Low frequency fatigue

Because a single twitch may be not a good indicator of peripheral fatigue, tetanic stimulations are sometimes conducted at different frequencies (from 5 to 100 Hz). Low frequency fatigue (LFF) i.e. a larger decrease of force evoked by stimulation at low versus high frequency with fatigue is generally considered to reflect excitation-contraction coupling failure [61]. For instance, a correlation between the depressed calcium release and a decrease in 20/50 Hz torque ratio has already been showed [62]. By evoking a tetanus at maximal intensity to the femoral nerve or at the motor point, previous authors did not find evidence of any LFF after prolonged skiing [30],

cycling [19] or running [8,9,11] exercises. These results could be surprising after prolonged running since muscular damage occurs. It has been showed that excitation-contraction coupling failure after eccentric exercise is due to physical and chemical disruption of the membrane systems involved in Ca^{2+} release [63] so that muscular damage and LFF are usually connected [64]. The lack of LFF in knee extensor muscles after prolonged running for 3h and more [e.g. 30 km [8], 4-h [4] or 5-h treadmill running [9] is consistent with an animal experiment showing that 90 min intermittent running downhill did not induce LFF in the rat *Soleus* muscle [65]. Although low-frequency fatigue was not observed for knee extensor muscle after prolonged running exercise, it was observed after an intense stretch-shortening cycle exercise [66] and cycling exercise performed at 75% $\dot{V}O_2$ max until exhaustion [14].

As the measurements in the fatigued state were usually performed almost immediately after the termination of the exercise [7, 8, 9, 65], the exercise may have potentiated the low-frequency evoked torque and thus may have hidden LFF [67]. As a consequence, the lack of LFF does not allow for complete certainty that the excitation-contraction coupling was not failed. Additional measurements of force at low- and high frequency still have to be performed 20-30 min after the exercise when potentiation caused by the exercise would have dissipated. In that sense, it has been shown that 1 h of running at 70% $\dot{V}O_2$ max decreased slightly but significantly the 20/50 Hz ratio evoked on triceps surae 15 min after the cessation of exercise [32]. However, Place et al [9] did not find any change in 20Hz tetanus and 20/80 Hz ratio 30 min after a 5-h running exercise. In this case, it seems improbable that running exercise had potentiated 20Hz tetanus and masked any low-frequency fatigue because potentiation lasts generally only a few minutes [68]. LFF can be due to : i) a reduction in Ca^{2+} release, ii) a decrease of myofibrillar Ca^{2+} sensitivity, iii) an increase of reactive oxygen species production [69] ; and may be a consequence of some damage to the structure of the muscle fiber and the excitation-contraction coupling [61]. However, the potentiated twitch observed following prolonged running exercise provided evidence for the lack of reduction in Ca^{2+} release during exercise and could explain the absence of low-frequency fatigue under certain conditions.

4. Changes in energy cost

Increase in oxygen uptake is usually observed throughout a prolonged exercise performed at a constant intensity. Davies and Thompson [4] reported a 9% increase in $\dot{V}O_2$ after a 4-h running exercise, while a 16% increase was observed during a marathon [70, 71]. Place et al [9] found also a 18%

decrease in running economy during a 5-h running. In contrast, Millet et al. [72] found no change in oxygen cost of running 15 min after the end of an 65km-ultramarathon and suggested that the subjects modified their movement pattern in order to decrease the mechanical cost of running in such long-term fatigue conditions. Increase of fat as an energy substrate, raised demand of body temperature regulation and changes in locomotor pattern are the most common explanations for the increase in the oxygen requirement during exercise [73]. The impaired neuromuscular function may contribute to the changes in locomotor pattern observed during prolonged exercise.

5. Summary

Previous research into fatigue after prolonged whole-body exercise suggest that there are likely multiple fatigue sites, both peripheral and central, although the most prominent changes following such exercises seem to originate at sites within the central nervous system. Indeed, some recent results provide strong evidence that central component of fatigue is predominant after 2-3 hours of exercise. Because prolonged exercises are rarely performed at a strict constant intensity but have frequently a stochastic nature including high-intensity epochs (sprints, up-hill …), reduction in maximal strength capacity may contribute to the decline in performance. Data suggest that even for grueling physical endeavour, fatigue is task dependent such that ultramarathon running may have different effects on neuromuscular functions in comparison to prolonged cycling exercise. It has previously been hypothesised that the relationship between neural and peripheral fatigue is a safety mechanism, whereby motor unit firing rate is reduced by the central nervous system to avoid excessive damage to the muscle fibres or to maintain whole body homeostasis [74, 75]. Whilst the exact mechanisms attributable to this central and peripheral fatigue cannot be definitively assigned, there is evidence of disruption to the contractile muscle machinery, especially after prolonged running, which is present in conjunction with fatigue at a spinal and supraspinal level. Further work examining multiple physiological systems during exercise, including afferent input and central command generation is needed to better understand the time course of impairment in central and peripheral processes during long-duration exercise.

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