

# Can Neuromuscular Fatigue Explain Running Strategies and Performance in Ultra-Marathons?

## The Flush Model

Guillaume Y. Millet<sup>1,2</sup>

1 Université de Lyon, F-42023, Saint-Etienne, France

2 Inserm U1042, Grenoble, F-38000, France

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### Abstract

While the industrialized world adopts a largely sedentary lifestyle, ultra-marathon running races have become increasingly popular in the last few years in many countries. The ability to run long distances is also considered to have played a role in human evolution. This makes the issue of ultra-long distance physiology important. In the ability to run multiples of 10 km (up to 1000 km in one stage), fatigue resistance is critical. Fatigue is generally defined as strength loss (i.e. a decrease in maximal voluntary contraction [MVC]), which is known to be dependent on the type of exercise. Critical task variables include the intensity and duration of the activity, both of which are very specific to ultra-endurance sports. They also include the muscle groups involved and the type of muscle contraction, two variables that depend on the sport under consideration. The first part of this article focuses on the central and peripheral causes of the alterations to neuromuscular function that occur in ultra-marathon running. Neuromuscular function evaluation requires measurements of MVCs and maximal electrical/magnetic stimulations; these provide an insight into the factors in the CNS and the muscles implicated in fatigue. However, such measurements do not necessarily predict how muscle

function may influence ultra-endurance running and whether this has an effect on speed regulation during a real competition (i.e. when pacing strategies are involved). In other words, the nature of the relationship between fatigue as measured using maximal contractions/stimulation and submaximal performance limitation/regulation is questionable. To investigate this issue, we are suggesting a holistic model in the second part of this article. This model can be applied to all endurance activities, but is specifically adapted to ultra-endurance running: the flush model. This model has the following four components: (i) the ball-cock (or buoy), which can be compared with the rate of perceived exertion, and can increase or decrease based on (ii) the filling rate and (iii) the water evacuated through the waste pipe, and (iv) a security reserve that allows the subject to prevent physiological damage. We are suggesting that central regulation is not only based on afferent signals arising from the muscles and peripheral organs, but is also dependent on peripheral fatigue and spinal/supraspinal inhibition (or disfacilitation) since these alterations imply a higher central drive for a given power output. This holistic model also explains how environmental conditions, sleep deprivation/mental fatigue, pain-killers or psychostimulants, cognitive or nutritional strategies may affect ultra-running performance.

## 1. Introduction

More than 30 000 articles have been published about fatigue. Limiting keywords to 'muscle' and 'fatigue' still gave us more than 12 000 articles. It is known that the magnitude and aetiology of fatigue depend on the exercise under consideration.<sup>[1]</sup> Critical task variables include the muscle activation pattern, the type of muscle group involved and, the type of muscle contraction. However, the intensity and duration of activity are probably among the most important factors. This article focuses on ultra-endurance running exercises, the so-called ultra-marathons.

Throughout the world (e.g. in the US, Europe, Japan, Korea, South Africa), ultra-marathons have become increasingly popular in the last few years. For example, Hoffman et al.<sup>[2]</sup> recently analysed the participation in 161 km ultra-marathons in North America and showed that the number of finishes increased exponentially over the period 1977–2008 through a combination of increases in the number of participants, average annual number of races completed by each individual, and number of races organized every year. It is considered that more than 30 000 runners took part in at least one ultra-marathon in France in

2009. There is no consensus about the definition of contemporary ultra-marathons; some authors consider it to be any distance greater than a marathon, while for others, it is any event that exceeds 4 hours<sup>[3]</sup> or 6 hours<sup>[4]</sup> in duration. Ultra-marathons can last for up to 40 hours or even several days (e.g. 6-day races) and are basically of two types: (i) ultra-marathons performed on a mostly flat road (24 hours, 100 km); and (ii) those run on varying terrains (e.g. 100 miles in the US). Contrary to what is usually claimed, ultra-marathon running is not new; the Six-Day Professional Pedestrian Races in London and New York have existed since the 1880s.<sup>[5]</sup> Importantly, the ability to run, rather than only walk, over long distances (i.e. without fatigue) may have played a role in human evolution.<sup>[6]</sup> For example, it has been suggested that endurance running may have helped hominids to exploit protein-rich resources. Thus, while endurance running is now primarily a form of recreation, its roots may be as ancient as the origin of the human genus.<sup>[6]</sup> This type of extreme event can also be seen as a testbed for ideas on how some people manage to perform physical feats at which others can only marvel.<sup>[7]</sup>

Several models of fatigue have been proposed in the literature. For example, Abbiss and Laursen<sup>[8]</sup> reviewed the following eight different models that

may be applied to prolonged cycling: cardiovascular/anaerobic, energy supply/energy depletion, neuromuscular fatigue, muscle trauma, biomechanical, thermoregulatory, psychological/motivational and the central governor model. All of these are interrelated. For example, changes in biomechanical patterns may be both the cause and consequence of neuromuscular fatigue, which is also influenced by modifications in cardiovascular/anaerobic metabolism, muscle trauma and thermal conditions, and all potentially associated with the central governor. Similarly, depending on the authors and the scientific field, central fatigue has been presented as a decrease in percentage maximal voluntary activation (%VA),<sup>[9]</sup> neurobiological modifications in the brain,<sup>[10]</sup> a modification of motor control<sup>[11]</sup> or alterations in cognitive function.<sup>[12]</sup>

In exercise physiology, most published articles have defined fatigue as strength loss (i.e. a decrease in maximal voluntary contraction [MVC]). Strength loss in the fatigued state is multifactorial and is generally divided into central (i.e. above the neuromuscular junction) and peripheral (muscular), these two origins being interdependent on the mediation of peripheral afferences. The central/peripheral distinction was already proposed by Bainbridge in 1931.<sup>[13]</sup> In this context, central fatigue is an altered ability of the CNS to recruit motor units at a higher discharge rate than the frequency of tetanic fusion. In other words, a decrease in maximal voluntary activation (i.e. central fatigue) might be due to a de-recruitment of motor units and/or a decrease of the discharge frequency beyond the frequency of tetanic fusion, both factors leading to force decline. Central fatigue is variably implicated in total fatigue. It has been shown that prolonged exercise is associated with a large decrease in %VA, especially with running.<sup>[14]</sup> However, the role of central fatigue and its supraspinal and spinal components in the cessation of exercise (if the intensity is fixed) or in performance (if the intensity is self-chosen) is not clear. The problem is further complicated by the fact that (i) environmental conditions such as hypoxia and hyperthermia may exacerbate central fatigue or perceived exertion,<sup>[15,16]</sup> two different forms of central alterations; and (ii) that mental

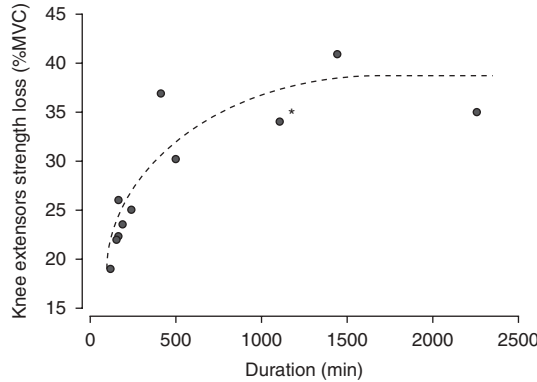
fatigue – another type of central alteration – has been demonstrated to play a role in performance limitation.<sup>[17]</sup> Although central fatigue is of great importance, this does not imply that peripheral fatigue is unimportant. How peripheral changes, central fatigue, environmental conditions and a runner's strategies (whether cognitive, nutritional or tactical) affect ultra-marathon performance and regulation of speed during a race has never been considered. Thus, the first aim of this article is to review the central and peripheral factors that might influence strength loss during very prolonged running exercise.

Describing these central and peripheral factors is essential but it does not predict how they affect submaximal muscle function during ultra-endurance running or how they influence speed regulation during a real competition (i.e. including pacing strategies). This poses the question of the relationship between fatigue evidenced by measures taken during maximal contractions/stimulation and performance limitation/regulation. The second aim of this article is then to propose a model that integrates these different parameters, including central and peripheral fatigue, which may help us to understand pacing strategies and performance during ultra-marathons. While the model is particularly well adapted to ultra-marathons, it can be applied to any type of endurance performance.

## 2. Neuromuscular Alterations in Ultra-Marathon Running

The alterations in neuromuscular function after prolonged running, cycling and skiing were reviewed by Millet and Lepers in 2004.<sup>[14]</sup> They focused on the origin of muscle fatigue after prolonged exercises lasting from 30 minutes to several hours. The authors showed that the knee extensors isometric strength loss increased in a non-linear way with exercise duration when running for longer than 2 hours. Since then, several articles have been published on this topic.<sup>[18-23]</sup> As shown in figure 1, the tendency toward no further decrease in knee extensor strength with increasing in running duration is confirmed.

Less is known about the decrease in peak power after prolonged running. Nevertheless, it



**Fig. 1.** Relationship between strength loss in the knee extensors expressed as a percentage of maximal voluntary contraction (%MVC) at rest and duration of running exercise.<sup>[18,19,23-30]</sup> \* Indicates the value is from unpublished observations.

has been reported that the decrease in counter-movement jump performance was around 45–60% of the knee extensors isometric MVC decrease after prolonged running.<sup>[19,24,25,31]</sup> Similarly, Lepers et al.<sup>[24]</sup> reported that isokinetic strength loss was smaller when measured over a concentric contraction compared with the eccentric or isometric mode.

### 2.1 Central Contribution

Methods such as the twitch interpolation technique, the ratio of electromyogram (EMG) signal during MVC normalized to the M-wave response (Mmax) or the comparison of the forces achieved with voluntary and electrically evoked contractions, have systematically shown that central fatigue largely contributes to muscle fatigue during long distance running.<sup>[20,22,25-27,32]</sup> It is known that the decrease in central activation occurring during exercise can be caused by several factors at the spinal (motoneuron properties, afferent input) and/or supraspinal levels.<sup>[9,33,34]</sup> A few studies have measured the changes in strength of muscles not involved in the exercise to further explore the origin of the lower central drive post-exercise.<sup>[20,27,32]</sup> It was hypothesized that a loss of grip strength after running would be a good indicator of supraspinal fatigue but no consistent changes were observed in grip strength following running exercise. Thus, this measurement did not

allow any conclusion of the existence or the absence of supraspinal fatigue after prolonged running because selective supraspinal fatigue may have occurred. Ohta et al.<sup>[35]</sup> investigated biochemical modifications during a 24-hour run and from indirect measurements such as serum serotonin and free tryptophan levels, they suggested that this type of exercise induces some supraspinal fatigue. It has been suggested for years that the accumulation of serotonin in several brain regions contributes to the development of fatigue during prolonged exercise.<sup>[36]</sup> This was thought to be due to an increase in the concentration ratio of free tryptophan to branched-chain amino acids because (i) branched-chain amino acids are oxidized; and (ii) higher plasma free fatty acids during prolonged exercise cause a parallel increase in free tryptophan since the free fatty acids displace tryptophan from their usual binding sites on albumin.<sup>[36]</sup> This in turn increases the concentration of free tryptophan (the serotonin precursor) in the brain. Meeusen et al.<sup>[10]</sup> went further suggesting that other neurotransmitters such as dopamine probably also play a significant role in supraspinal fatigue. Nevertheless, to the best of our knowledge, no study has clearly shown any evidence of central fatigue (e.g. a depressed %VA) with an increased serotonin/dopamine ratio or other biochemical changes in the CNS. Meeusen et al.<sup>[10]</sup> acknowledged that fatigue is probably due to a complex interaction between

central and peripheral mechanisms. It is worth noting that we recently observed a significant correlation between %VA changes during a 24-hour treadmill run for plantar flexor and knee extensor muscles,<sup>[26]</sup> which could be indicative of a common supraspinal mechanism regulating the neural drive to the working muscle. Another possibility is that hyperventilation lowers the arterial carbon dioxide tension and blunts the increase in cerebral blood flow, which can lead to an inadequate oxygen delivery to the brain and contribute to the development of fatigue.<sup>[37]</sup> Nevertheless, this is less likely to occur during ultra-marathons, because of the relatively low level of ventilation.

While some central activation deficit has been observed for knee extensor muscles in cycling,<sup>[38]</sup> there is a lower level of central fatigue after activities that result in less muscle damage than do running.<sup>[39]</sup> When marathon skiing<sup>[40]</sup> and 30-km running<sup>[27]</sup> in similar competitive conditions and duration were compared, the decrease in %VA was more pronounced for running than for skiing. Millet and Lepers<sup>[14]</sup> suggested that this result indicated spinal modulation rather than cortical alteration after the running exercise. Data from reflex measurements, such as the Hoffmann reflex (Hmax), provide interesting insights into the origin of central fatigue. The Hmax/Mmax ratio has been used as an indicator of motoneuronal excitability, and more generally to evidence modulations of neural drive at the spinal level.<sup>[41]</sup> This index was found to decline during a 24-hour treadmill run and was correlated with decreases in MVC and %VA, especially at the end of the exercise (personal observation). This finding concurs with those of Racinais et al.<sup>[20]</sup> who reported depressed H-reflexes after a 90-minute run. This could be due to reduced motoneurone excitability or pre-synaptic inhibition. In both cases, inhibitory mechanisms could be limiting muscle force production. Such inhibitory action may result from thin afferent fibre (group III–IV) signalling, which may have been sensitized by the production of pro-inflammatory mediators, produced during prolonged exercise.<sup>[42–46]</sup> So, while supraspinal fatigue may play a role in reduced neural drive after prolonged exercises, it can be suggested that spinal adaptation, such as inhibi-

tion from type III and IV group afferents or disfacilitation from muscle spindles contributes to this reduced central drive. Group III–IV afferent fibres may also contribute to the submaximal output from the motor cortex (see Taylor et al.<sup>[47]</sup>). Taken together, this suggests that high central fatigue due to prolonged running is not due solely to CNS biochemical changes but that afferent fibres are probably involved. The twitch interpolation technique at the peripheral nerve does not allow discrimination between central fatigue originating from a supraspinal site and/or from the spinal level. Researchers at the Prince of Wales Medical Research Institute in Sydney (e.g. Todd et al.<sup>[48]</sup>) have measured supraspinal deficit by superimposing magnetic stimulations of the motor cortex to voluntary contractions. Recently, this method has been used to demonstrate the existence of supraspinal %VA alteration in the quadriceps after cycling exercise and prolonged MVCs.<sup>[49,50]</sup> Future studies should use this new method to further investigate central fatigue after ultra-distance running exercises.

## 2.2 Alterations at the Muscle Level

Central fatigue alone cannot explain the entire strength loss after prolonged running exercises. Alterations of neuromuscular propagation, failure of excitation-contraction coupling and modifications in the intrinsic capability of force production may also be involved. To the best of our knowledge, there has been no measure of change in action potential conduction velocity using high-density EMG after prolonged running exercise. Information about the propagation of the action potentials can then only be deduced from changes in the M-wave characteristics. This is problematic,<sup>[51]</sup> especially in the case of ultra-marathons, since muscle oedema and sweat can complicate interpretation of the Mmax. Limits also exist for mechanical twitch responses after ultra-marathons,<sup>[14]</sup> in particular the fact that fully potentiated twitches were not always used in the past (e.g. Millet et al.<sup>[25]</sup>). Tetanic responses are slight or not influenced by potentiation. A significant but moderate (~10%) decrease in high-frequency force response has been found for knee

extensors after prolonged<sup>[27]</sup> or ultra-long<sup>[26]</sup> running exercise.

Indirect indices of muscle damage (creatine kinase, myoglobin, C-reactive protein, myosin heavy chain fragments, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, cytokines) also suggest the existence of some peripheral alterations<sup>[26,44-46,52-54]</sup> but from the few results available, it appears that subjects show wide variability in the degree of muscle damage.<sup>[26]</sup> Potential explanations for this variability in inter-individual response include differences in genes, training (particularly the repeated bout effect,<sup>[55]</sup> that likely occurs, particularly during downhill running training<sup>[56]</sup>) flexibility, oxidative stress,<sup>[18]</sup> muscle fibre type<sup>[57]</sup> and running technique. No direct evidence exists to preferentially support any one factor and it is probably a combination of them all that explains the large difference in muscle damage among subjects. Nevertheless, for the last two potential factors (i.e. typology and running technique), it is interesting to report that (i) there was no significant relationship between knee extensor peripheral fatigue and percentage type I muscle fibres in the *vastus lateralis*;<sup>[26]</sup> and that (ii) ultra-long running (from Paris to Beijing [i.e. 8500 km in 161 days, ~53 km daily]) modified the running patterns towards a 'smoother' style in one case study.<sup>[58]</sup> This latter point was evidenced by (i) a higher stride frequency and duty factor; (ii) a reduced aerial time with no change in contact time; (iii) a lower maximal vertical force and loading rate at impact; and (iv) a decrease in both potential and kinetic energy changes at each step.<sup>[58]</sup> We also measured a reduced running economy after the trip. Thus, even if it is possible that the running pattern changes could be linked to the decrease in maximal strength also observed, we suggested that running pattern modification was a strategy to reduce the potential deleterious effects of his ultra-long distance run rather than to decrease the energy cost of running. Further studies should also examine the potential influence of running technique on muscle damage during ultra-endurance running, particularly when running on variable terrain (trails). Anecdotal information from qualified coaches suggests that technical ability in

downhill sections might be a real determinant of fatigue and performance.

Low-frequency fatigue (LFF; also called prolonged low-frequency force depression<sup>[59]</sup>) [i.e. the preferential loss of force at low frequencies of electrical stimulation] is a prominent characteristic of exercises involving lengthening contractions of the active muscles such as eccentric- and stretch shortening cycle-type exercises,<sup>[60]</sup> and has been associated with failure of the excitation-contraction coupling.<sup>[61]</sup> Contrary to what is generally observed after downhill running,<sup>[56,62]</sup> most studies did not show LFF after prolonged running exercise despite several experiments that have measured this factor during ultra-long running exercises including the recent 24-hour treadmill study.<sup>[26-28,32]</sup> Only recently have we been able to measure LFF after one of the most extreme exercises realized by humans in race conditions: a 166-km mountain ultra-marathon with 9500 m of positive and negative elevation change.<sup>[23]</sup> It can then be suggested that minimal exercise intensity is required to induce mechanical or metabolic disturbances that can result in developing LFF. However, there is a limitation in that it is theoretically possible that axonal hyperpolarization preferentially depresses the high-frequency response during tetanic muscle stimulation. Thus, an absence of modification to the low- to high-frequency ratio could have resulted from the combined effects of LFF, which preferentially depresses low-frequency response, and hyperpolarization, which preferentially depresses high-frequency response.<sup>[26]</sup>

### 3. The Flush Model

Measuring central activation changes or force/EMG responses during MVCs or electrically evoked stimulation after prolonged running gives some insight into the potential factors implicated in fatigue at the CNS and/or muscle level. However, it does not predict how this affects submaximal muscle function during ultra-endurance running or how this influences speed regulation during a real competition when pacing strategies are allowed. This poses the question whether there is any relationship between fatigue evidenced by



measures taken during maximal contractions/stimulation and performance limitation/regulation. Before answering this question, the change in power output during ultra-marathons must first be described.

### 3.1 Power Output Change in Ultra-Marathon Runners

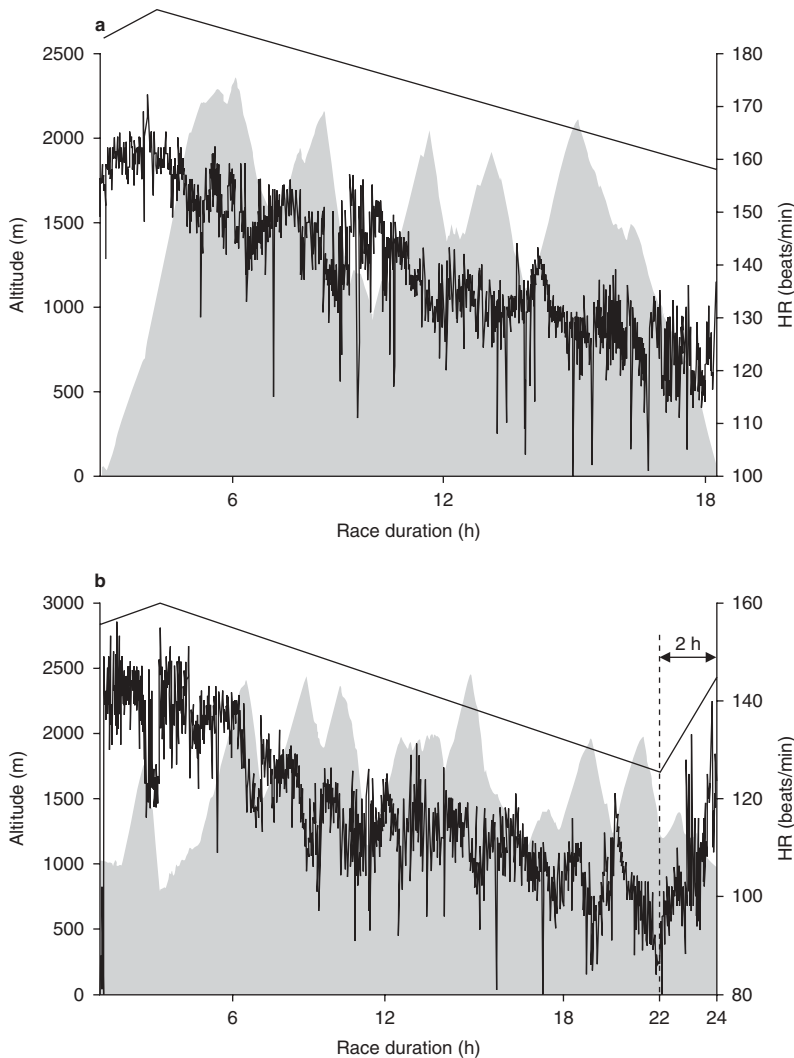
Only one study<sup>[31]</sup> has examined the changes in efficiency/energy cost to determine whether power output can be connected to speed. Since it is unlikely that a large uncoupling exists between power output and velocity, monitoring the speed change over flat-course ultra-marathons (the typical event being the 24-hour race) gives an excellent idea of the mechanical power produced by the runner. During a self-paced 24-hour treadmill run where the subjects were asked to give their best performance as they would in a normal race, Martin et al.<sup>[26]</sup> showed a clear decrease in velocity during the first 16 hours before there was a tendency for this to level off. Over a shorter distance (68 km) in a real competition, Utter et al.<sup>[63]</sup> showed that subjects reached a rating of perceived exertion (RPE) similar to the subjects of Martin et al.<sup>[26]</sup> (i.e.  $15.4 \pm 0.4$ ) but there was an increase of RPE up to the end of the race. While several studies have investigated 24-hour races,<sup>[64-66]</sup> we are not aware of any data reporting velocity changes during an official race. Anecdotal evidence and personal data suggest that speed is reduced during ultra-marathons, even in elite athletes. Also, unpublished results showed that the speed of the top five runners in the 2007 French 24-hour championship had a tendency to decrease but that this was less pronounced for the winner. Over a shorter distance (100 km at the 1995 International Association of Ultra Runners World Challenge), Lambert et al.<sup>[67]</sup> reported that the best runners (i) reduced their initial speed less and later in the race; and (ii) they showed less variation in their speeds than did their lesser-performing counterparts. The general tendency was still that these 107 runners reduced their speed over time.<sup>[67]</sup> In marathon running, it has been reported<sup>[68]</sup> that some elite athletes are able to maintain their pace throughout the race but

their slower counterparts (especially young men<sup>[69]</sup>) slow down over the distance.

It is more difficult to document power output and speed change during ultra-trails (i.e. off-road ultra-marathons) since the terrain is usually hilly, even mountainous. Future studies should measure the changes in speed at given slopes using global positioning system tools. Data from Utter et al.<sup>[63]</sup> nevertheless suggest that heart rate (HR) decreases over a 68-km ultra-marathon. Personal data also show that HR generally decreases over an ultra-endurance race in mountains (see figure 2a and the first 22 hours in figure 2b) and that a correlation exists between change in HR and change in elevation speed (in m/hour) similar to the relationship seen between change in HR and speed variation after the first 10 km of a marathon.<sup>[70]</sup> When using HR to predict speed variations, one should also consider the HR drift with fatigue (i.e. HR increases at a given speed). This is visible in the first 1–2 hours in figure 2 but the change in HR due to cardiac drift is less than the speed variation. However, any decrease in HR during competitions can also only be due to a decreased power output.

### 3.2 Description of the Model

Despite the lack of systematic studies on speed change over ultra-marathons, the data presented strongly suggest that power output/speed decreases with time in ultra-marathon running, even in elite athletes. Following the initial question about the relationship between fatigue as evidenced by measures taken during maximal contractions/stimulations and performance limitation/regulation, one should then ask whether the decreased speed is due to strength loss. Based on the fact that knee extensor and plantar flexor muscle strength decreased by ~30–40% and since the force developed at each step is very low, it does not appear that strength loss can directly explain this speed reduction. Marcora et al.<sup>[71,72]</sup> suggested that the locomotor muscles' capacity for force production is always well above the requirements of high-intensity cycling, which is about 20% of MVC. In other words, even if this point has been debated,<sup>[73]</sup> failure to produce the force/power required by



**Fig. 2.** Typical heart rate (HR) changes during two mountain ultra-marathon races: one crossing the island of la Reunion (155 km [a]) and one around the Mont-Blanc (165 km [b]). The global tendency of heart change is indicated by the solid line. The profile of the course is also given (grey shading).

the exercise despite maximal voluntary effort does not seem to limit submaximal performance as commonly assumed.

While it is not possible to predict to what extent the fatigue mechanisms identified during maximal isometric contractions would affect performance during an ultra-endurance running event, it may nevertheless be hypothesized that there is an indirect effect. As proposed by the tele-

oanticipatory system<sup>[74]</sup> or the central governor model,<sup>[75,76]</sup> the level of muscle activation (and so the speed) is thought to be progressively reduced to keep the RPE during running below a maximum tolerated level<sup>[26]</sup> (i.e. to maintain the body below a homeostatically acceptable exercise intensity).<sup>[77,78]</sup> In relation to the data presented above regarding central and peripheral fatigue, the last part of the present article will discuss

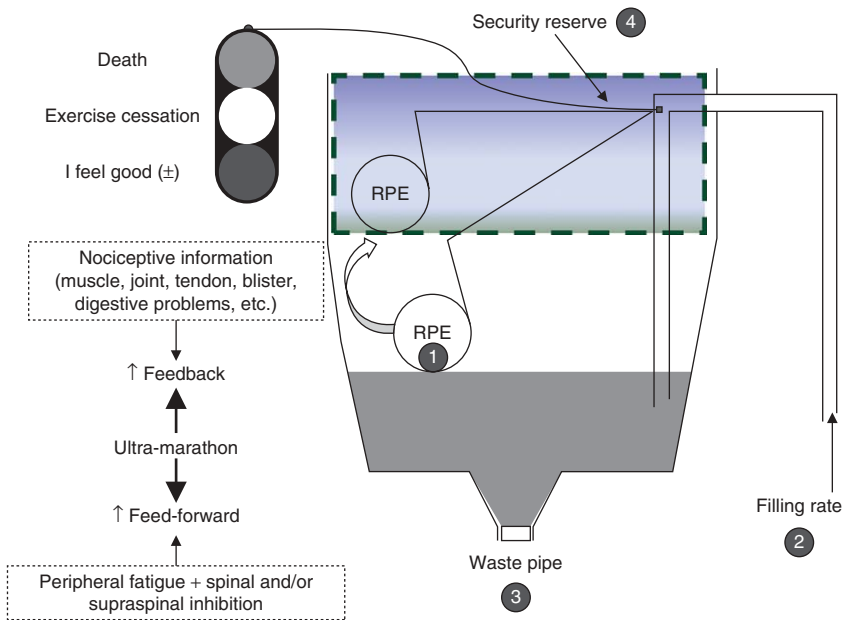


(i) how RPE is progressively increased with time for a constant (or even lower) running speed; and (ii) how in relation to changes in environmental conditions, sleep deprivation/mental fatigue, drugs, cognitive or nutritional strategies, this may regulate performance in ultra-marathon running. We propose a conceptual model based on the flush toilet (figure 3). The ‘flush model’ is based on the central governor model proposed by Noakes et al.<sup>[76]</sup> (i.e. agrees with the fact that exercise performance is regulated by the CNS specifically to prevent catastrophic physiological failure). However, the flush model emphasizes the importance of peripheral fatigue that has been described in detail in the first part of the present article. Also, because it has been suggested that the central governor integrate the input from various systems all related to exercise,<sup>[79]</sup> the flush model was also built to take into account changes not associated with exercise. The present model was mainly designed to explain the role of fatigue on perfor-

mance in ultra-marathon running and consists of four components: the ball [or buoy, (1) in figure 3] represents RPE and can increase or decrease based on the filling rate (2) and the water evacuated through the waste pipe (3). There is also a security reserve (4), also called the emergency reserve,<sup>[80]</sup> which allows the subject to prevent physiological harm.<sup>[81]</sup> We believe that the flush model can help us to understand running strategies during an ultra-marathon, but a few questions must first be addressed.

### 3.3 Feed-Forward and Feedback Mechanisms Influence the Filling Rate

First, what influences the filling rate? At the beginning of an ultra-marathon, running pace is based on a control system which estimates the optimal power output.<sup>[82]</sup> Depending on the runner, his or her goal may be either simply finishing the race, finishing the race in a certain time



**Fig. 3.** The flush model. Rating of perceived exertion (RPE) is assimilated to the volume of water in the tank (i.e. an increase in volume of water signifies a higher RPE and decreasing the level of water in the tank indicates decreasing RPE). The water can get in (filling rate, 2) and out (via waste pipe, 3) and the level of water can be detected by the ball (1). The level of water depends on the filling rate, mainly determined by peripheral changes and central inhibition/disfacilitation (feedback and feed-forward mechanisms), but other factors such as mental fatigue, nutritional strategies, sleep deprivation, environmental conditions and exceptional events during races can affect the level. The size of the security reserve (4) is mainly determined by motivation. Psychostimulants and pain killers can modify the sensitivity of the RPE sensor (i.e. the ball).

or being well placed at the finish (for instance being in the top ten runners). The estimation is based on several factors such as distance, elevation, environmental conditions, training status and runability (i.e. technical difficulty) of the course. This teleanticipation means that the runner has a template that contains existing data on exercise performance (the so-called 'experience' or personal history of running). In fact, Ulmer<sup>[82]</sup> considers that this template may be inborn but it is generally accepted that optimal pacing strategy is the result of a learning process.<sup>[67]</sup> The initial pace gives an initial filling rate of the tank and the higher the initial speed for a given running, the faster the filling rate. This is mainly due to both feed-forward and feedback mechanisms.

Feedback mechanisms have been widely documented in the literature. For instance, Amann et al.<sup>[83]</sup> nicely showed that by attenuating the ascending activity of nociceptive and metaboreceptive A $\delta$  (group III) and C fibres (group IV), somatosensory feedback from the locomotor muscles influences central motor drive. Even if this experimental study has been criticized for lack of proper placebo procedures,<sup>[84]</sup> the authors concluded that locomotor muscle afferent feedback, which also facilitates performance through optimizing muscle oxygen delivery,<sup>[85]</sup> exerted an inhibitory influence on the determination of central motor drive during high-intensity exercise. While acidosis or inorganic phosphate accumulation is unlikely to occur in ultra-marathon running, other biochemical mediators, such as the accumulation of extracellular potassium<sup>[86]</sup> or cytokines (especially interleukin-6 and its antagonist IL-1ra) due to structural muscle damage<sup>[44-46]</sup> (see section 2.2 about peripheral fatigue), could trigger group III/IV afferent fibres and mediate the sensation of fatigue.<sup>[74]</sup> Nociceptive information is much more complicated; there is a potential role for pain arising not only from the muscles but also from other sites such as joints and tendons. Even blisters (cutaneous afferences<sup>[87]</sup>) or digestive problems<sup>[42]</sup> could all potentially play a role. For shorter distances (i.e. higher intensity and ventilation rate), dyspnoea may also be involved in nociceptive information<sup>[88]</sup> but probably not in ultra-marathon running. It should also be noted

that a modest temporary reduction in pressure pain perception was observed after a 100-mile (161-km) trail run, only in the faster runners.<sup>[89]</sup> Although the subject is debated,<sup>[85]</sup> feedback from the locomotor muscles probably plays a major role in central motor drive regulation in ultra-marathons. As stated in section 2.1, the down-regulation of group III/IV afferents at the spinal and supra-spinal levels<sup>[90]</sup> is a probable explanation for why maximal %VA is lower after running than after cycling or skiing for similar intensity/distance.<sup>[14]</sup>

While afferent feedback certainly has a key function, the regulation of central motor command is complex and also depends on the environment. For example, altitude and elevated temperature are two conditions frequently encountered by ultra-marathon runners (e.g. races in Nepal or in deserts). Regarding altitude, using a sub-maximal test until exhaustion in hypoxia/normoxia while the muscles were maintained in identical complete ischaemic conditions, we showed that (i) inhibitory mechanisms from working muscles play a major role in the cessation of the exercise in hypoxia and that (ii) a minor but significant direct effect of inspired oxygen fraction on the CNS could potentiate this limiting mechanism and explain why performance was slightly reduced in hypoxia.<sup>[15]</sup> Similarly, Amann et al.<sup>[91]</sup> showed that peripheral fatigue measured with femoral nerve magnetic stimulation at task failure was substantially less severe in hypoxia compared with normoxia or moderate hypoxia. This was attributed to brain hypoxic effects on effort perception, leading the subjects to stop earlier. Similar conclusions can be deduced from hypoglycaemia<sup>[92]</sup> or hyperthermia experiments. Regarding this latter factor, it is worth noting that high temperature does not alter performance over brief contractions but does cause reductions during sustained contractions<sup>[16]</sup> or prolonged exercises.<sup>[93]</sup>

Thus, sensory feedback contributes to central fatigue and effort perception, presumably through its indirect projection into the anterior cingulate cortex.<sup>[85]</sup> Other authors have argued that sensory signals from peripheral receptors do not contribute to perception of effort but generate other sensations experienced during exercise (e.g. muscle

pain and thermal sensation<sup>[84,94]</sup>). In all cases, the increase in RPE with fatigue is not abolished by spinal blockade of somatosensory feedback from the muscles; there must be other mechanisms. Besides triggering inhibitory mechanisms, peripheral fatigue implies that greater muscle activation is required for a given mechanical power to be produced in the fatigued condition. Indeed, at a given force or power output, the onset of fatigue is usually concomitant with a rise in neuromuscular cost (EMG signal amplitude), which points to the recruitment of additional motor units and/or a higher discharge rate in order to compensate for peripheral alterations. It is known that RPE changes and the increase in muscle activity during a constant-load exercise are correlated.<sup>[95]</sup> Marcora et al.<sup>[71]</sup> showed that the reduced locomotor muscle force after drop jumps resulted in a higher RPE at a given power output and a reduced time to exhaustion during high-intensity constant-power cycling. They suggested that the effects were mediated by the increased central motor command required to exercise with weaker locomotor muscles,<sup>[71]</sup> which increased the perception of effort probably throughout its corollary discharge to sensory areas of the brain.<sup>[84]</sup> Similarly, Gagnon et al.<sup>[96]</sup> tested the effects of pre-induced quadriceps fatigue (using electrostimulation) on endurance performance of healthy individuals and patients with chronic obstructive pulmonary disease. These authors demonstrated that endurance time significantly decreased by 20–25% in the experimental condition in both groups. There has been hot debate about the role of afferent feedback from fatigued locomotor muscles as an important determinant of endurance exercise performance.<sup>[84,85]</sup> Gagnon et al.<sup>[96]</sup> suggested that the enhanced metaboreflex is not the main mechanism through which exercise tolerance was reduced in the fatigued state in both study populations.

Moreover, a change in muscle efficiency after ultra-marathon running<sup>[31]</sup> can affect muscle recruitment to maintain a given task. Spinal inhibition and/or disfacilitation (see section 2.1) after ultra-marathon running could also necessitate higher central command (i.e. reinforcing feed-forward mechanisms) from supraspinal sites. Finally, the

gain of motoneurons decreases in fatigued conditions such that additional synaptic drive at a premotoneuronal level is required to maintain a constant firing rate<sup>[91]</sup> (i.e. a larger descending drive is needed to continue exercise at the same power output). So, as well as the nociceptive signal coming from the peripheral receptors, these feed-forward mechanisms (also called the ‘sense of effort’<sup>[1,79]</sup>) could also partly explain the RPE drift.<sup>[97]</sup>

Interestingly, RPE for the same exercise could vary with environmental conditions and is not necessarily associated with a decrease in MVC (e.g. at altitude).<sup>[98]</sup> In summary, the initial pace and the adjustments made in response to these feed-forward and feedback mechanisms<sup>[81]</sup> directly affect filling rate. RPE is probably affected by both central command output and muscle afferents.<sup>[85]</sup> In other words, as stated by Smirmaul,<sup>[94]</sup> an interaction between the sense of effort and the sensations obtained from afferent sensory feedback that is probably the ultimate regulator of exercise performance. We suggest that for ultra-marathons performed over hilly terrain, feed-forward and feedback mechanisms are mainly implicated in uphill/flat sections and downhill sections, respectively.

#### 3.4 Apart from the Filling Rate, Which Factors Influence the Quantity of Water?

The second question is whether the volume of water (absolute RPE) depends only on the filling rate? The answer is clearly no. It has recently been argued that it is an interaction between the sense of effort and the sensations obtained from afferent sensory feedback that is probably the ultimate regulator of exercise performance.<sup>[94]</sup> However, while these two factors certainly play a crucial role, it is, for example, possible to start an exercise with more water in the tank than usual (i.e. with a higher RPE at the beginning of exercise than is normally the case). Indeed, it is possible to feel some fatigue without any exhaustive physical load, for example, after a stressful day. More importantly, Marcora et al.<sup>[17]</sup> reported that the time to exhaustion at 80% of peak power output was significantly reduced by ~15% after 90 minutes of a demanding cognitive task. This was associated with a higher RPE at the beginning of the

cycling exercise compared with the control condition. Since RPE increased similarly over time in both conditions, mentally fatigued subjects reached their maximal tolerated RPE and disengaged from the cycling exercise earlier than did the controls.<sup>[17]</sup>

Similarly, although one night of sleep deprivation does not usually affect MVC or intense exercise,<sup>[99]</sup> several studies have demonstrated a deleterious effect on endurance performance.<sup>[100,101]</sup> Interestingly, a higher RPE for a given load has been observed after sleep deprivation.<sup>[99,100,102]</sup> Some authors<sup>[100,101]</sup> showed that, after sleep deprivation, subjects ran a shorter distance during a 30-minute self-paced treadmill exercise than did their controls, yet their perception of effort was similar. The authors suggested that altered perception of effort may account for decreased endurance performance after sleep deprivation. Other data show that RPE is not only dependant on sensory information and cortical output. For example, unknown or unexpected running exercise duration may affect RPE,<sup>[103]</sup> suggesting that RPE has an affective component. Also, changing the tempo of music that cyclists were listening to influenced their self-chosen power and cadence.<sup>[104]</sup> In summary, effort perception probably involves the integration of multiple signals from a variety of perceptual cues. Alternatively, as suggested in section 3.6 for the amphetamines or pain killers, it can be argued that perception is a complex neurocognitive process that does not depend only on the intensity of the sensory signal because sensory signals are processed at brain level and interpreted by the subject. It is then possible that mental fatigue, music and sleep deprivation affect the processing of sensory signals rather than provide additional sensory signals. Nevertheless, in that case, the rate of increase in RPE (filling rate) would be changed rather than RPE at the beginning of the exercise, as is the case, for example, for mental fatigue.<sup>[17]</sup>

### 3.5 The Waste Pipe

The third question is whether rest is the only way to decrease the level of water in the tank. It is the most obvious but probably not the only one. For example, it may be possible to reduce the

water level while running using suitable psychological strategies.<sup>[105]</sup> Various psychological routines can be used by runners to attenuate the discomfort of intense physical exertion. These strategies, labelled 'dissociative thoughts' (i.e. the runner distracts him-/herself by thoughts of a more external nature) are performed to diminish the sensations of pain during a marathon.<sup>[105]</sup> Nevertheless, it has been reported that the best marathon runners adopt associative cognitive strategies (i.e. are centered on their own sensations),<sup>[106]</sup> probably with the goal of maintaining optimal running technique/efficiency and so decreasing peripheral fatigue (and the filling rate). Another way to decrease the level of water in the tank might be nutritional strategies. Chambers et al.<sup>[107]</sup> recently showed that rinsing the mouth with solutions containing glucose and maltodextrin could improve cycling performance. The authors suggested that this could be due to activation of brain regions involved in reward and motor control since functional MRI measurements showed that these regions believed to mediate emotional and behavioural responses to a rewarding sensory stimulus were activated. Thus, in addition to its peripheral action (i.e. slowing the tank filling rate), glucose ingestion could have some central effects (i.e. decreasing the water level). Unidentified oral receptors in the mouth could counteract the increase in RPE, permitting higher central command and power output.

Interestingly, the suggestion of downhill cycling through hypnotic manipulation decreased RPE without altering exercise HR or blood pressure responses.<sup>[108]</sup> One could also suggest that reducing maximal neural drive (i.e. central fatigue, a decrease in %VA) may reduce the size of the tank. In this context, Sogaard et al.<sup>[109]</sup> acknowledged that central fatigue can only be demonstrated during MVCs, but these authors suggested that a decrease in %VA may have contributed to the increase in RPE during sustained low-intensity contractions (i.e. 15% MVC for 43 minutes). They based this speculation on the fact that central fatigue was among the factors that predicted RPE changes. To our knowledge, no neurophysiological basis exists regarding the potential role of central fatigue to explain at least in part the RPE changes.

### 3.6 The Security Reserve

The fourth question is why exercise stops (in the case of a time to exhaustion) or why the runner decides to adjust his or her speed/power output (in the case of a time trial). Assuming a constant level of motivation, exercise cessation appears to occur at the same RPE whatever the rising slope<sup>[110-112]</sup> and the starting level.<sup>[17,71]</sup> Marcora et al.<sup>[17]</sup> have incorporated Brehm's theory – a general motivation theory that does not specifically refer to exercise – to propose a psychobiological model of endurance performance. Marcora et al.'s model postulates that subjects decide to withdraw effort (i.e. disengage) when an exercise is perceived to be either too difficult or the effort demanded exceeds the upper limit of what people are willing to invest. Alternatively, it has been proposed that exercise terminates when the feelings of discomfort overwhelm the potential rewards of continuing to exercise.<sup>[112]</sup> This was reviewed in 2003 by Kayser.<sup>[79]</sup> It is interesting to report that an opiate antagonist, naloxone, leads to significant reductions in exercise performance when compared with control trial.<sup>[113]</sup> The authors of the article concluded that working capacity was limited by the individual RPE, which can be attenuated by endogenous opioids rather than by physiological fatigue. Thus, it is not task failure but task disengagement that sets the exercise limit before reaching the security reserve. Even in highly motivated competitors, task disengagement always occurs before there is a threat to life.<sup>[79]</sup> Humans do not usually exceed their security reserve. There are a few exceptions where dramatic loss in body homeostasis was reached causing collapse such as during marathons or triathlons (e.g. Gabriela Andersen-Schiess in the 1984 Olympics or Julie Moss in the 1982 Hawaii Ironman), especially in (i) hot environments with subjects not always familiar with these environmental conditions (i.e. unadapted template/sensor efficiency); or (ii) under the effect of psychostimulants (e.g. Tom Simpson who died).

One could pose the question whether elite athletes finish with a lower security reserve. While the common belief is that better athletes can 'dig deeper' and work relatively harder than their less

successful counterparts,<sup>[70]</sup> we are not aware of any scientific study supporting this concept. One indirect argument has been proposed by Esteve-Lanao et al.<sup>[70]</sup> who found that the pattern of percentage maximum heart rate ( $\%HR_{max}$ ) response during an event was very similar in athletes with large differences in running performance. These authors concluded that better runners are faster due to their underlying physiological capacity rather than to their ability to put greater relative effort into their competition. Studies investigating the percentage of maximal oxygen uptake ( $\dot{V}O_{2max}$ ) sustained during competition in function of the level of performance are contradictory. It was found that the faster running speed of the more trained runners over 10–90 km was not due a higher  $\% \dot{V}O_{2max}$  during competition but was due to their superior running economy.<sup>[114]</sup> In contrast, performance was significantly related to the specific endurance (i.e. the average speed sustained over a 24-hour running exercise expressed in  $\% \dot{V}O_{2max}$ ).<sup>[57]</sup> Nevertheless, a higher  $\% \dot{V}O_{2max}$  or  $\%HR_{max}$  sustained during competition does not necessarily mean that the elite athletes can 'dig deeper' since this may be due to physiological differences in terms of endurance. Further studies must examine this interesting question.

A very important factor in the flush model is that the sensor may be deregulated (i.e. the interpretation of the incoming signal may be affected).<sup>[115]</sup> In other words, the processing of sensory signals is affected rather than additional sensory signals provided. This is true in two opposing cases: amphetamines<sup>[80]</sup> (or more generally when dopaminergic system is manipulated<sup>[115]</sup>) and pain killers,<sup>[83,116]</sup> both of which induce higher peripheral fatigue and/or metabolic disruptions. For example, higher lactate/HR<sup>[80,116]</sup> or lower peak doublet response to a magnetic stimulation at the cessation of exercise has been reported.<sup>[83]</sup> Interestingly, while more anecdotal, Amann et al.<sup>[83]</sup> reported that all their subjects needed assistance in disembarking the cycling ergometer after injection of intrathecal fentanyl. In the evening (i.e. several hours after exercise cessation), their subjects reported continuing problems with ambulation and muscle soreness, which had never been



observed in any of the many other studies requesting exhaustion conducted in that laboratory.<sup>[83]</sup> It should be noted that psychostimulants (e.g. amphetamines, cocaine) could act by providing a pleasure sensation (i.e. water leak throughout the waste pipe rather than sensor deregulated). Some runners, even elite athletes, use local anaesthetics/anti-inflammatory drugs (e.g. Tissugel® in France), particularly applied to the knee joint. While this is not prohibited by the World Anti-Doping Agency policy, the flush model suggests that this may be beneficial for improving performance in ultra-marathon running.

According to the flush model, there is always a reserve for muscle recruitment (the security reserve) that can be used for the so-called 'end spurt'<sup>[117]</sup> when the runner is at his or her highest level of peripheral fatigue. In ultra-marathons, this is clearly illustrated in figure 2b representing the HR data of an ultra-marathon runner performing a race around the Mont-Blanc. In this example, very particular race conditions (from 11th to 6th place with opponents regularly announced as potential targets) led the runner to accelerate at the end of the race when his muscle fatigue was higher than at ~22 hours. This further illustrates that central regulation is not totally based on peripheral changes. Since RPE was not recorded, it is not possible to say whether this was related to the enjoyment of overtaking several opponents near the finish line, which counteracted the sensation of fatigue (i.e. the same level of water despite increasing the power output with some water being evacuated through the waste pipe) and/or a decrease in the security reserve due to increased motivation.

While mental processes are important in all sports, it is probably particularly true for ultra-marathon runners. Weir et al.<sup>[118]</sup> suggested that the central governor is most applicable to endurance exercise since the decline in muscle performance under intensely fatiguing exercise conditions can be directly attributed to peripheral fatigue. It is further possible that for shorter distances, the organism is equipped with a system to protect its integrity, but at a peripheral level.<sup>[79]</sup> For example, glycogen depletion may alter excitation-contraction coupling, which in turn limits muscle

contraction capacity and so restricts muscle damage. Also, it has been suggested that for exercise of several minutes duration, RPE is increased by sleep deprivation but when it is as short as 30 seconds, sleep deprivation causes only a small change in the perception of exercise intensity<sup>[99]</sup> and thus no reduction in performance. Marino et al.<sup>[119]</sup> recently argued that events such as the marathon and, for example, walking 1000 km are both quantitatively and qualitatively different, and not simply because the 1000 km race is longer. They proposed that it could be that the limits to performance in a 1000-km race are predominantly mental, while the limits to performance in the marathon are predominantly physiological. Thus, it can be suggested that ultra-marathon running is an interesting model to study central regulation of exercise. We believe that all interventions designed to manipulate RPE and the sensation of discomfort are of particular interest in this sport.

#### 4. Conclusion

As Marino et al.<sup>[119]</sup> recently pointed out, Mosso concluded in his book *La fatica* (fatigue) published 120 years ago,<sup>[120]</sup> that two phenomena categorize fatigue, the diminution of muscular force and the sensation of fatigue: "That is to say, we have a physical fact which can be measured and compared and a psychic fact which eludes measurement." Thus, the study of fatigue should address both the perception of effort and the decline in force that occurs during sustained exercise.<sup>[1]</sup> The aim of the present article was to review these two aspects of fatigue and to propose a model that integrates the 'neuromuscular' and 'physiological' factors of fatigue (responsible for maximal force reduction) in ultra-marathon running to explain the regulation of performance. It has been argued<sup>[76,79,121]</sup> that fatigue can be understood as a highly regulated strategy conserving cellular integrity, function and, indeed, survival. The flush model, dedicated to integrating the fatigue mechanisms in ultra-marathon performance (and more generally to any type of endurance performance), using a holistic approach, is fully compatible with this statement.



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Correspondence: Professor *Guillaume Millet*, Laboratoire de Physiologie de l'Exercice (EA 4338), Médecine du Sport-Myologie, Hôpital Bellevue, 42055 Saint Etienne, Cedex 2, France.

E-mail: [guillaume.millet@univ-st-etienne.fr](mailto:guillaume.millet@univ-st-etienne.fr)

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