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Neuromuscular fatigue during whole body exercise

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This short review offers a general summary of the consequences of whole body exercise on neuromuscular fatigue pertaining to the locomotor musculature. Research from the past two decades have shown that whole body exercise causes considerable peripheral and central fatigue. Three determinants characteristic for locomotor exercise are discussed, namely, pulmonary system limitations, neural feedback mechanisms, and mental/psychological influences. We also discuss existing data suggesting that the impact of whole body exercise is not limited to locomotor muscles, but can also impair non-locomotor muscles, such as respiratory and cardiac muscles, and other limb muscles not directly contributing to the task.

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Introduction

Fatigue is a psychophysical phenomenon which can originate from occupational and recreational activities and results in a decreased physical and/or cognitive performance [1]. Of special interest for this review is neuromuscular fatigue, defined here as an exercise-induced reduction in the force/power-generating capacity of a muscle or muscle group [2]. The vast majority of the literature examining exercise-induced fatigue has taken a reductionist approach, focusing on single-joint exercise modalities. While this approach is important for our basic understanding of fatigue, it eliminates the interaction and influence of various biological systems on the development of neuromuscular fatigue. As this lack of integration leaves the findings from single-joint studies with rather limited functional relevance, a progressively increasing number of studies have now been focusing on the impact of whole body exercise, which is characterized by significant engagement and interaction of various biological systems. The purpose of this brief review is to offer an overall summary of the impact of whole body exercise on neuromuscular fatigue and to highlight selected, task-specific determinants. Given the mandated length of this review, factors such as environmental influences [3,4], aging [5], and disease [6,7], all of which can greatly impact the development of fatigue during locomotor exercise, will not be discussed.

Mechanisms and quantification of neuromuscular fatigue

Neuromuscular fatigue is determined by a peripheral and a central component. Peripheral fatigue results from processes at or distal to the neuromuscular junction that lead to a reduction in force or power output in response to a given neural input [8–10]. A detailed description of the cellular mechanisms determining peripheral fatigue is offered elsewhere [11,12]. While there are different methods to quantify peripheral fatigue *in vivo* [13], a supramaximal electrical or magnetic peripheral motor nerve stimulation to evoke a twitch force generated by the target muscle is generally employed (e.g. stimulation of the femoral nerve to evoke a quadriceps twitch force) before and shortly after a given task. The exercise-induced difference in twitch force is used to quantify peripheral fatigue. Importantly, the fall in twitch force from before to immediately after exercise is highly correlated with intramuscular metabolic perturbations [14•].

Central fatigue entails processes within the central nervous system (CNS) that reduce neural drive to the muscle and result in a decrease in voluntary muscle activation and therefore a decline in force or power and a compromised performance [15,16]. Reductions in neural drive can result from changes at premotor regions of the brain [17] and/or within the motor pathway (i.e. the motor cortex and spinal motoneurons) [18]. Voluntary activation is traditionally quantified via the twitch interpolation technique [19]. This method involves a supramaximal peripheral nerve stimulation during a maximal voluntary contraction (MVC), which, if muscle activation is submaximal, evokes an additional involuntary force termed the superimposed twitch. The amplitude of the superimposed twitch is then expressed as a ratio with the potentiated twitch immediately following the same MVC. Pre-exercise to post-exercise reductions in voluntary activation are generally accepted to reflect central fatigue. Nonetheless, it is important to recognize that a primary limitation of this assessment is that it is conducted during an isometric, single-joint contraction performed before and after the actual task and may therefore not be a good indicator of muscle activation and central fatigue present during whole body exercise. Alternatively, locomotor muscle electromyography (EMG), when normalized to sarcolemma excitability (i.e. normalized to m-waves), offers a more appropriate surrogate for motoneuronal output and muscle activation *during* locomotor exercise. However, it is critical to consider that changes in conduction velocity and amplitude cancellation can also influence EMG, which has raised considerable criticism of EMG as an estimate of neural drive/motoneuronal output (for review see Farina *et al.* [20]).

Whole body exercise causes locomotor muscle fatigue

Locomotor muscle fatigue develops during whole body exercise (cycling [21,22]), rowing [23], running [24,25], cross-country skiing [26], simulated sporting events [27]) ranging from 12 s to 5^{+} hour [24,28]. Current data suggest that peripheral fatigue develops before central fatigue during maximal [29] and submaximal exercise [28,30–32]. However, it is unclear as to whether central or peripheral mechanisms are primarily responsible for the termination of exercise at task failure [22,33].

The magnitude of fatigue within a task has been proposed to be dependent upon the exercise duration and intensity, such that more peripheral fatigue is observed following shorter, more intense exercises while more central fatigue is observed following longer duration exercises [34•]. However, more recent work has found that the degree of end-exercise fatigue may be independent of the duration of exercise when a locomotor task is performed within the severe exercise intensity domain (i.e. similar after 3 min and 12 min of cycling to task failure [35]). Nevertheless, exhaustive whole body exercise generally results in an approximate 25–45% reduction in quadriceps twitch force (i.e. peripheral fatigue) and an approximate 5–12% decrease in VA (i.e. central fatigue, [5,14•,36,37]). While these exercise-induced changes are much smaller compared to those induced by single-joint exercise (Figure 1), it is sufficient to compromise whole body exercise performance [21] and therefore of considerable significance. Finally, although endurance exercise training can attenuate the development of fatigue during exercise of a given absolute workrate [39,40•], it is currently unclear how training affects the development of fatigue during a given relative intensity.

Determinants of locomotor muscle fatigue during whole body exercise

Pulmonary system

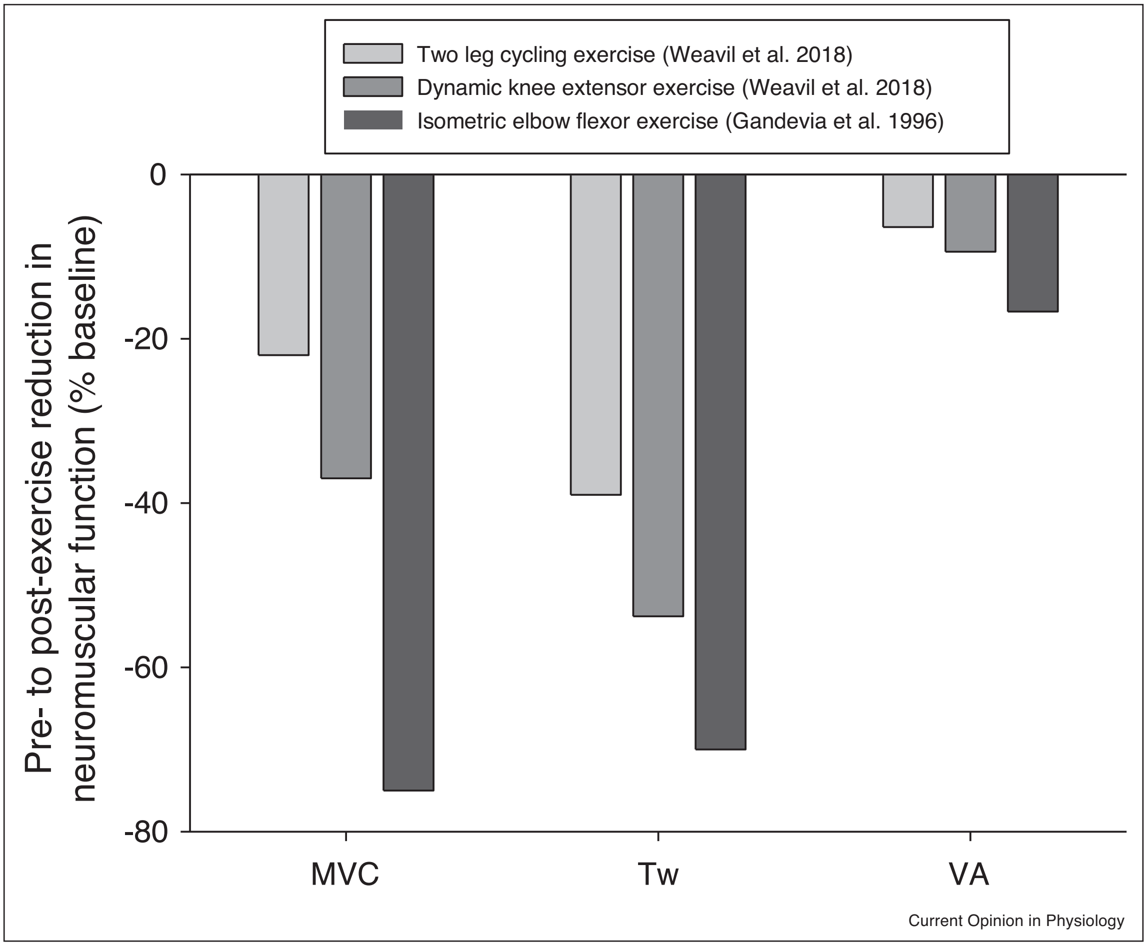
The primary objectives of the pulmonary system during exercise are to maintain arterial PO_2 close to, and to prevent arterial PCO_2 from rising much above, resting values while minimizing respiratory muscle work. The pulmonary demands associated with whole body exercise have the potential to compromise these objectives and thereby accentuate the development of locomotor muscle fatigue (for review Ref. [41]). Three pulmonary system limitations have previously been documented to exacerbate the development of locomotor muscle fatigue during whole body endurance exercise.

First, high-intensity exercise can decrease arterial O_2 saturation by 5–15% from resting values (hemoglobin saturation ~98%), a phenomenon referred to as exercise-induced arterial hypoxemia [42]. Factors determining arterial desaturation during exercise include an inadequate compensatory hyperventilation, acid-induced and temperature-induced shifts in O_2 dissociation at any given arterial PO_2, and an excessive widening of the alveolar to arterial O_2 difference [42]. The resultant arterial desaturation compromises O_2 delivery to the locomotor muscle and, given the importance of convective O_2 delivery in determining exercise-induced fatigue [43], promotes the development of peripheral fatigue [44].

Second, respiratory muscle fatigue associated with the high levels of respiratory muscle work during strenuous whole body exercise has been recognized as a significant contributor to locomotor muscle fatigue in both health [45,46,47•] and disease [7]. The mechanism linking fatiguing respiratory muscle work and locomotor muscle fatigue is termed the respiratory muscle metaboreflex. Briefly, fatiguing respiratory muscle contractions and associated accumulation of metabolites within the inspiratory and expiratory muscles activate metabosensitive phrenic afferents [48], which reflexively increases sympathetic vasoconstrictor activity [49] restricting blood flow and O_2 delivery to the exercising limb [50,51]. The significance of this mechanisms was demonstrated by using a proportional assist ventilator to unload the respiratory muscles during strenuous cycling exercise. In the face of a 60–70% decrease in inspiratory muscle work, end-exercise locomotor muscle fatigue was reduced by 40–50% ([45,46,47•], Figure 2) and cycling performance was significantly improved [52]. Considering the sex differences within the structure of the pulmonary system (e.g. smaller airways [53]), attenuating respiratory muscle work in females may have an even greater effect on mitigating locomotor muscle fatigue compared to males [47•].

Finally, limited data in humans suggest that large intrathoracic pressure swings during exercise can alter cardiac output and subsequently influence locomotor muscle O_2 delivery [54,55]. For example, the normally occurring negative intrathoracic pressures during cycling exercise enhance venous return and, in turn, stroke volume and cardiac output [54]. In contrast, even only moderate increases in positive intrathoracic pressures on expiration

Figure 1



Contrasting the amount of neuromuscular fatigue resulting from different exercise modalities. Note the smaller degree of end-exercise fatigue associated with whole body exercise compared to both dynamic and isometric single-joint exercise. MVC, maximal voluntary contraction; Tw, potentiated twitch force; VA, voluntary activation. Data adapted from Weavil *et al.* [5] and Gandevia *et al.* [38].

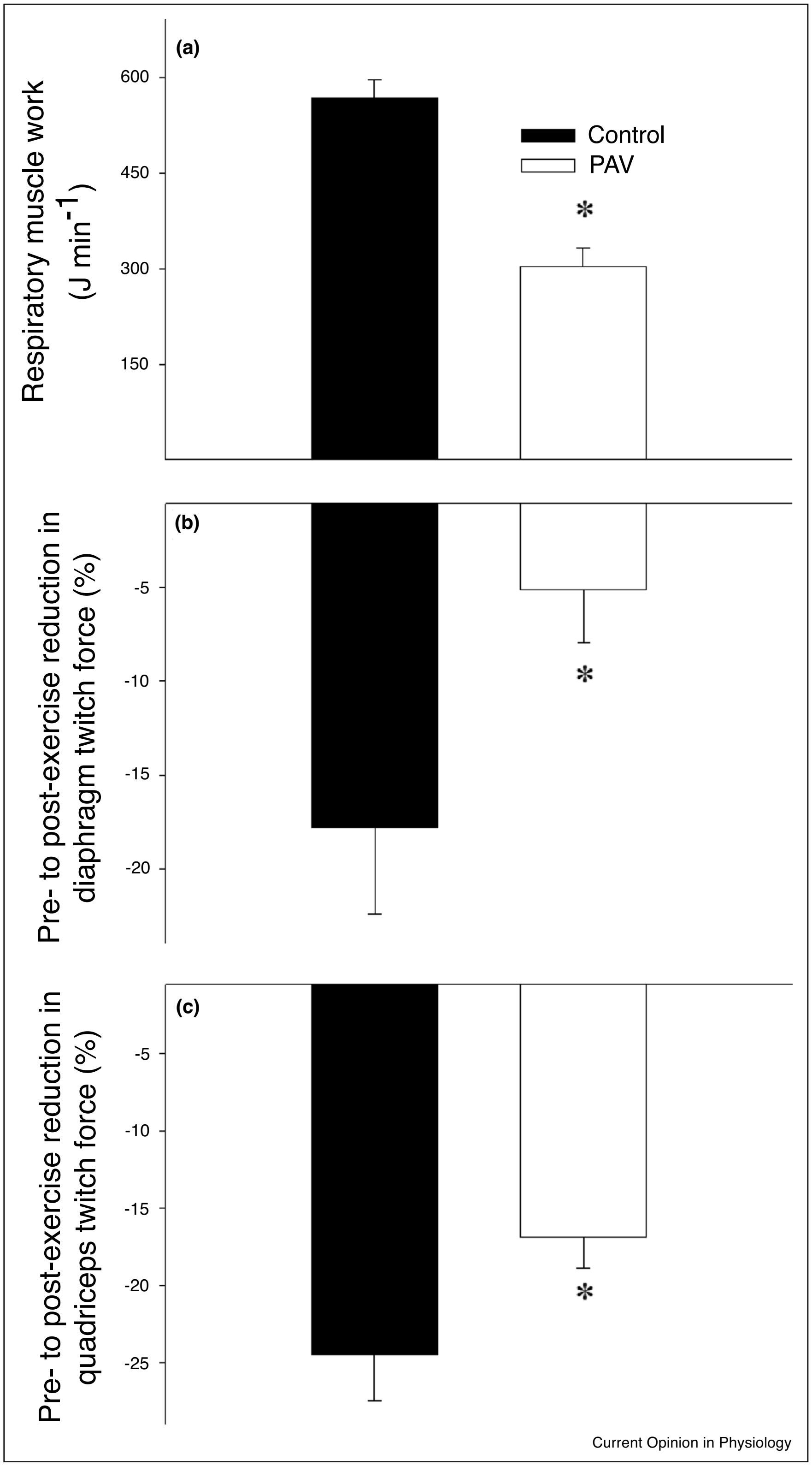
(10–15 cm H_2O) can decrease ventricular transmural pressure which reduces the rate of ventricular filling during diastole and thereby impairs stroke volume and cardiac output [55,56]. Increases in expiratory positive intrathoracic pressures of similar, or even greater magnitudes, can occur during the transition from moderate to intense exercise in well-trained individuals and/or with the development of expiratory flow limitations [57], particularly in pulmonary disease populations. However, evidence for a direct effect of intrathoracic pressures on locomotor muscle fatigue is currently lacking.

Group III/IV-mediated afferent feedback from locomotor muscle

Metabosensitive and mechanosensitive group III/IV locomotor muscle afferents project, both directly and indirectly, to cortical and spinal regions of the central nervous system [58–60]. The influence of these afferents on the development of locomotor muscle fatigue during whole body exercise has been examined by pharmacologically attenuating feedback from these sensory neurons. By using a μ-opioid receptor agonist (e.g. lumbar intrathecal fentanyl), which attenuates approximately 60% of group III/IV muscle afferent feedback from the legs [61,62], it has been shown that these neurons exert two distinct influences on locomotor muscle fatigue during whole body exercise [63]. First, group III/IV afferents minimize the development of peripheral fatigue by enhancing cardiac output, locomotor muscle perfusion pressure, and ventilation during whole body exercise [64,65]. This feedback-mediated cardiovascular and ventilatory augmentation is critical for assuring adequate O_2 delivery to the locomotor muscle and, subsequently, peripheral fatigue resistance and performance [64].

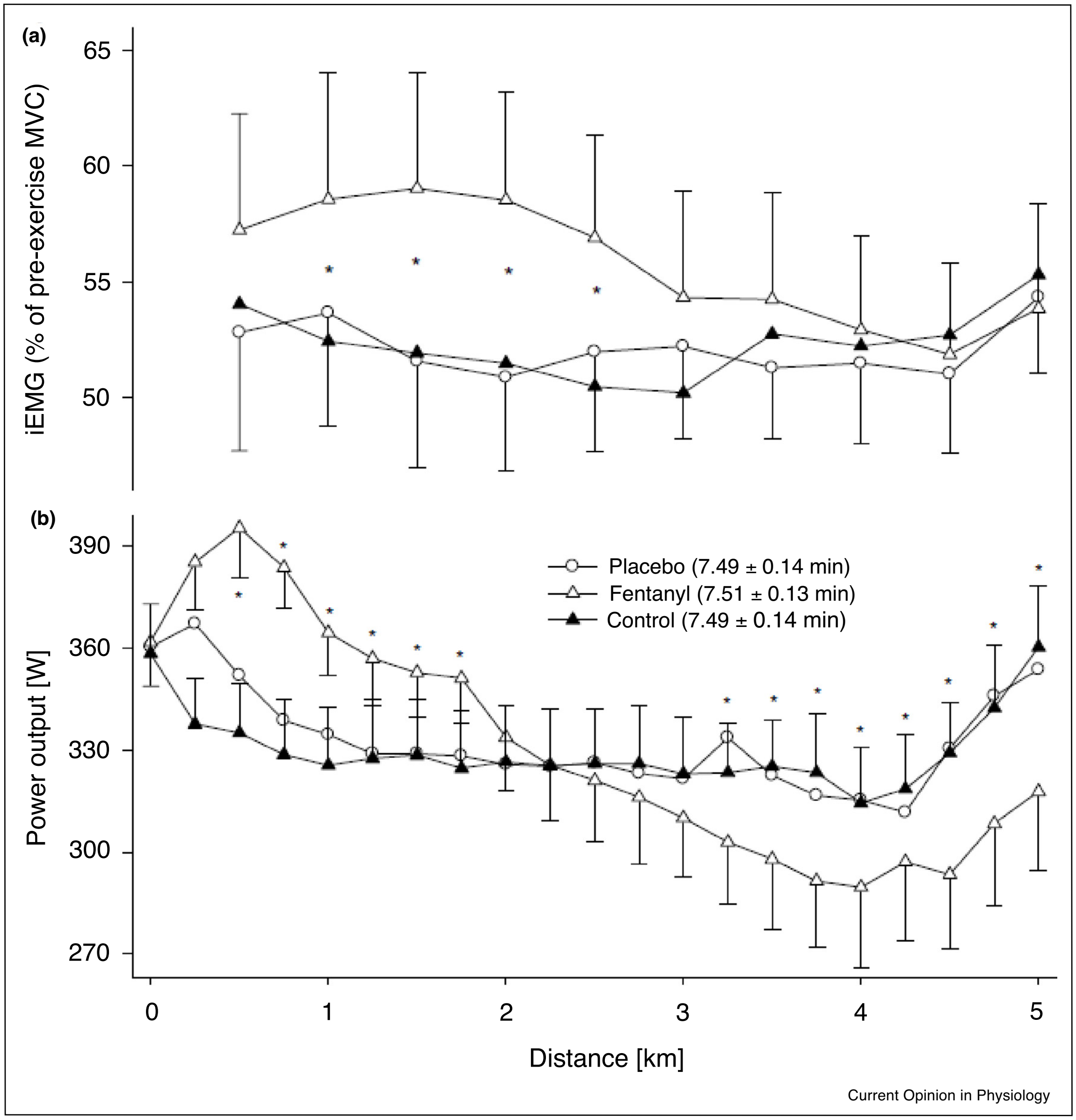
Second, studies using afferent blockade have shown that feedback from group III/IV locomotor muscle afferents restrict the output from spinal motoneurons and muscle activation during cycling exercise (Figure 3; [14•,61,66]). Interestingly, this inhibitory influence originating from

Figure 2



During the same constant-load cycling task, a proportional assist ventilator (PAV) reduces respiratory work **(a)** and subsequently attenuates peripheral fatigue of the inspiratory **(b)** and locomotor **(c)** muscles in men. *Denotes significant difference from Control. Data adapted from Dominelli *et al.* [47•].

Figure 3



Graphic illustration of the effect of attenuating group III/IV muscle afferent feedback on neural drive **(a)** and power output **(b)** during a 5 km cycling time trial. EMG was averaged every 0.5 km whereas power output was reported every 0.25 km. Intrathecal fentanyl increased mean integrated EMG (iEMG) compared to control and placebo (subcutaneous saline infusion at lumbar level) exercise. * Denotes significant difference between Fentanyl and Placebo conditions. Data from Amann *et al.* [61].

exercising leg muscles is also present in muscles not directly involved in the locomotor task (e.g. cycling exercise impairs elbow flexor voluntary activation; [67]). Although the exact mechanisms determining the afferent feedback-mediated reduction in spinal motoneuron output are not fully understood, it is thought that group III/IV muscle afferents exert inhibitory influences on voluntary descending drive 'upstream' of the motor cortex [68] and disfacilitate corticospinal excitability during cycling exercise [66,69•]. Regardless, the afferent-mediated central inhibition has been proposed to represent a potential regulatory mechanism therein preventing an excessive exercise-induced homeostatic challenge in working limb muscle [14•,70]. Indeed, when muscle afferent activity is attenuated via intrathecal fentanyl during cycling exercise, both intramuscular metabolic perturbation and peripheral fatigue of the quadriceps exceed levels observed in control conditions [14•,61] and result in temporary ambulatory issues [61]. Further details on the role of group III/IV muscle afferents in regulating exercise performance by influencing the development of peripheral fatigue and the 'sensory tolerance limit' can be found elsewhere [71].

Mental/psychological influences

Mental fatigue is characterized by a subjective feeling of tiredness or impaired commitment to continue a task arising from cognitively challenging activities [72]. Despite some controversy [73,74], mental fatigue has been suggested to compromise whole body endurance performance without affecting resting neuromuscular function or the cardiopulmonary response to exercise [75–77]. Yet, mental fatigue was shown to exacerbate the conscious sensation of exertion (i.e. rating of perception of effort) during whole body exercise and, given its potential role in limiting endurance performance [78], was therefore considered the main factor mediating the mental stress-induced decrease in cycling performance [79]. This idea is, perhaps, corroborated by the lack of performance impairment with mental fatigue during short, anaerobic exercise characterized by maximal effort throughout [73].

Whole body exercise causes respiratory and cardiac muscle fatigue

The high ventilatory demands associated with strenuous whole body exercise can impact neuromuscular function of the respiratory muscles. Indeed, the ventilatory response during whole body exercise performed at intensities $\geq$85% of VO_2 max [80] can cause considerable central and peripheral fatigue [81,82] in both inspiratory (i.e. diaphragm [47•,80]; Figure 2) and expiratory (i.e. abdominal; [82,83]) muscles. Interestingly, however, when the same ventilatory work is mimicked at rest, diaphragmatic fatigue does not occur [84], likely because O_2 delivery to the diaphragm is adequate compared to during locomotor exercise and/or the absence of acidosis associated with whole body exercise [84]. This explanation is supported by the observation that experimental decreases in convective O_2 delivery, via a hypoxic inspirate, exacerbate respiratory muscle fatigue during isocapnic voluntary hyperpnoea performed at rest [85]. Importantly, although the ventilatory response to locomotor exercise remains adequate in the presence of respiratory muscle fatigue [81,86], whole body exercise performance is impaired [46,86,45].

Furthermore, there is echocardiographic evidence suggesting that prolonged exercise (>120 min; i.e. marathon running, Ironman triathlon) can impair cardiac function and cause cardiac fatigue (for review Ref. [87]). Diminished cardiac function following exercise have been attributed to impaired left and right ventricle systole and diastole, changes in cardiac loading, cardiomyocyte damage, and reduced β-adrenergic sensitivity [87]. While this effect is transient, repeated cardiac fatigue may predispose endurance athletes to ventricular arrhythmias secondary to deleterious cardiac remodeling [88].

Summary

The past two decades have seen an increased emphasis on studies investigating the influence of whole body exercise on neuromuscular function. Locomotor exercise results in significant peripheral and central fatigue, which, together, impair endurance performance in proportion to the degree of fatigue. Furthermore, whole body exercise not only impairs locomotor muscle function, but can also induce significant fatigue of respiratory, cardiac, and limb muscles not directly involved in the task.

Conflict of interest statement

Nothing declared.

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