Performance fatigability is not regulated to a peripheral critical threshold

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Short title: Fatigability is task-dependent

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ABSTRACT

The critical threshold hypothesis proposes that performance fatigability during high-intensity exercise is tightly regulated by negative-feedback signals from the active muscles. We propose that performance fatigability is simply dependent on the exercise mode and intensity; the consequent adjustments, in skeletal muscle and the other physiological systems that support exercise, interact to modulate fatigue and determine exercise tolerance.

KEY WORDS

Afferent feedback; cardiovascular; exercise; fatigue; fatigability; muscle; respiratory

SUMMARY

The magnitude of performance fatigability observed after high-intensity exercise is task-dependent, and not regulated to a peripheral critical threshold.

KEY POINTS

• Fatigue is a symptom, or percept, that limits exercise performance in healthy individuals.

• The critical threshold hypothesis emphasizes a critical role for metabolite-mediated afferent discharge in determining exercise tolerance. Specifically, negative-feedback signals from active muscle act to restrain central motor command to limit metabolic perturbation within locomotor muscle, and therefore constrain decrements in the quadriceps potentiated twitch force (a measure of performance fatigability) to a specific, task-dependent level.
We propose that performance fatigability is simply determined by the mode and intensity of the task; these factors dictate the active muscle mass, and demand on other physiological systems. The consequent adjustments interact to modulate fatigue, which determines exercise tolerance.

We review existing correlative and experimental evidence to demonstrate that performance fatigability of skeletal muscle is but one limiting factor in modulating fatigue and exercise tolerance, the importance of which varies with the exercise task.
INTRODUCTION

The study of fatigue and the factors that limit, or regulate, exercise performance has captivated scientists for centuries, but a thorough explanation of the etiology of this condition remains elusive (1, 2). The classic writings of Angelo Mosso (3) identified the two phenomena that characterize fatigue; i) a physical component represented by a diminution of muscular force, and ii) fatigue as a sensation. Over a century later, debate still ensues over our understanding of fatigue, and specifically the sensation of fatigue. Mosso’s original description of fatigue was based on the concept of repetitive contractions that induced neuromuscular adjustments in healthy populations that were reversible by rest. This idea of an organic cause for a perceptual construct remains pertinent for our conceptualization of fatigue in the exercise sciences (4). For the purpose of this review fatigue will be discussed within the taxonomy proposed by Enoka & Duchateau (2). Specifically, fatigue is defined as a symptom or percept, characterized by feelings of tiredness and weakness, in which physical and cognitive function are limited by interactions between performance fatigability and perceived fatigability (2). Performance fatigability refers to the decline in an objective measure of performance; such as the production of maximal voluntary force, the ability to provide an adequate signal to voluntary activate muscle, or the involuntary twitch response to stimulation (2). Throughout this review, we will use the reduction in the involuntary twitch force in response to motor nerve stimulation as our indicator of performance fatigability. Perceived fatigability refers to the sensations that regulate the integrity of the performer; these sensations can be modulated by disruptions to homeostasis (e.g. core temperature, hydration status, substrate availability) and modifications in psychological state (e.g. arousal, motivation, mood) that contribute to the perception of effort required for the task (2). Performance and perceived
fatigability are interdependent, and interact to modulate and determine the symptoms of fatigue. In healthy participants, the physiological adjustments associated with high intensity exercise are strongly associated with perceived fatigability and changes in the rating of perceived exertion (RPE), such that there is a tolerable degree of fatigue the person performing the exercise is willing to experience at any given point during an exercise task. Such a definition is similar to the idea of a sensory tolerance limit (5, 6), but emphasizes the myriad of modulating factors, both physical and psychological, that could contribute to the symptom of fatigue the exerciser is willing to endure at any given point during an exercise challenge.

The critical threshold hypothesis proposes a pivotal role for metabolite-mediated afferent discharge in regulating ‘central motor command’ (defined as the activity of premotor and motor areas of the brain related to voluntary muscle action; 7) during exercise, and thus exercise performance. This hypothesis proposes that adjustments in contractile function are constrained during high-intensity exercise in healthy participants by negative-feedback signals from active muscles. Specifically, exercise-induced alterations of the intramuscular metabolic milieu are proposed to provoke inhibitory input from group III and IV afferents that act to restrain central motor command in order to protect against excessive disruption to muscle homeostasis (8). This hypothesis has been experimentally tested via studying the decline in the electrically or magnetically evoked twitch response to motor nerve stimulation as an indicator of fatigue-related changes in the muscle. A number of studies (e.g. 8, 9, 10-17) have observed an unvarying post-exercise reduction in the involuntary quadriceps potentiated twitch amplitude ($Q_{tw,pot}$, often defined as peripheral fatigue, or locomotor muscle fatigue, but hereafter referred to as performance fatigability) to a range of
exercise tasks and experimental interventions, and provided interpretations in support of this concept.

Recently, the authors of the critical threshold hypothesis revisited the sensory tolerance limit concept proposed by Gandevia (6) to offer a more holistic explanation for understanding the limits to exercise tolerance (5). The sensory tolerance limit concept proposes it is the sum of all neural feedback, feedforward signals, and associated sensations that interact to limit exercise performance. Such an idea is qualitatively similar to the taxonomy proposed by Enoka & Duchateau (2) discussed previously. This notwithstanding, the idea that group III/IV afferent feedback acts to reduce central motor command and the subsequent development of performance fatigability to a specific level remains a key feature of these updated proposals, but with an acknowledgement that the magnitude of adjustments varies between individuals and the exercise task (5).

The aim of this review is to propose that performance fatigability is not constrained to a task-specific, critical peripheral threshold, but rather simply depends on the muscle mass engaged during the task, and the associated disruption to homeostasis in multiple physiological systems. The muscle mass recruited during exercise is dependent on the intensity and mode of the task; these two critical factors will dictate the magnitude of performance fatigability. Specifically, we propose that for the same mode of exercise, reductions in $Q_{tw,pot}$ will increase with exercise intensity, primarily because a greater proportion of the active musculature will be activated and exhausted as the force requirements of the task increase. Furthermore, we propose the adjustments as the active muscle mass increases during different exercise modes (e.g.
single limb < double limb < whole body locomotor) are progressively dictated by the
demand placed on maintaining the homeostasis of other competing physiological
systems that support exercise (e.g. cardiovascular, respiratory). As a consequence, the
magnitude of performance fatigability is lower as other adjustments contribute to the
maximum tolerable symptom of fatigue the exerciser is willing to endure. We propose
the observation of a consistent magnitude of end-exercise performance fatigability is
due to the characteristics of the task, and not a result of regulation to a critical
threshold. Disruption to the metabolic milieu of the muscle tissue is but one potential
modifier of fatigue, and varies in importance depending on the exercise task. This
notwithstanding, the ability of skeletal muscle to meet the demands of exercise is
likely to be the primary modulator of fatigue and thus exercise performance, as
skeletal muscle will incur greater metabolic stress relative to it’s maximum capacity
in comparison to the cardiac and respiratory muscle systems that support exercise
(18). This elegant design feature of the human body ensures that the homeostatic
physiological systems responsible for supporting life, do not approach exhaustion
during, and continue maintaining homeostatic functions after, exhaustive exercise
(18). However, while skeletal muscle will typically be the primary limiter of exercise,
the increased demand on cardiac and respiratory muscle systems, particularly at the
point of task failure, will still contribute to modulating the symptom of fatigue.
Ultimately, we propose it is the percept of fatigue that is regulated during exercise,
derived by changes in the factors that modulate performance and perceived
fatigability, which will vary in their importance depending on the exercise task.
These ideas are explicated in this review, alongside a reinterpretation of the
correlative and experimental evidence that seemingly supports the critical threshold
hypothesis.
Performance fatigability and active muscle mass

For the same relative intensity, we propose the magnitude of active muscle mass required for the exercise task will modulate the degree of performance fatigability, because of the consequent challenge to whole-body homeostasis that will contribute to the tolerable magnitude of fatigue. Data from comparisons between modes of exercise within (13, 14), and between studies (9, 19-21) support this idea.

Rossman et al. (13, 14) directly investigated the effect of varying the active muscle mass on the magnitude of end-exercise performance fatigability. In the first of these studies (14), participants voluntarily exercised to the limit of tolerance at 85% of modality-specific maximal intensity in two exercise modes; isoinertial knee extension, and locomotor cycling exercise. The magnitude of performance fatigability was higher after knee extensor exercise when the active muscle mass was small, compared to cycling exercise when the active muscle mass was larger (−53 ± 2 vs. −34 ± 2% reduction in Q\textsubscript{tw,pot}, respectively). The same authors subsequently confirmed these observations studying single-leg knee extension exercise compared to double-leg knee extension exercise, thereby circumventing the potential confounding factor of mode-specific exercise responses (13). Specifically, participants completed single-leg and double-leg knee extension exercise to their self-determined limit of tolerance at the same relative modality-specific exercise intensity. The magnitude of performance fatigability was higher after single leg knee extension exercise (−44 ± 6%) compared to double-leg knee extension exercise (−33 ± 7%). In both studies the higher active muscle mass was also concurrent with higher cardiorespiratory responses (13, 14), and in the second of these studies, the increase in the vastus
lateralis integrated electromyogram signal (iEMG) from the first to the last minute of exercise, was higher during single-leg compared to double-leg exercise (147 ± 24 vs. 85 ± 15%) indicative of a progressively greater recruitment of additional muscle mass during the single-leg trial. These data demonstrate that when the active muscle mass is smaller, a greater proportion of the available musculature is engaged during the task, and the demand on other physiological systems is lower. In concert, these factors lead to a greater post-exercise reduction in Q_{tw,pot}, as the exerciser can tolerate greater local muscular stress before the perception of effort becomes excessive.

Further comparisons between exercise modes also illustrates how the active muscle mass modulates performance fatigability. For high intensity cycling exercise (80-90% of peak intensity measured during an incremental test to the limit of tolerance, usually abbreviated as P_{max}) numerous research groups, including our own, have shown a relatively consistent post-exercise reduction in potentiated twitch force of approximately 35% (8, 9, 19, 20, 22). When the task requires a smaller active muscle mass, the absolute reduction in twitch force after exhaustive exercise is higher. For example, we observed a reduction in Q_{tw,pot} of 60 ± 13% after 3 × 30 s MVCs (23), and as previously demonstrated Rossman et al. (13, 14) reported absolute reductions in Q_{tw,pot} of 44% and 53% after single limb knee extension exercise. Conversely, during running exercise, when the active skeletal muscle mass is increased, the absolute decline in potentiated twitch is lower; even for maximal repeated sprint exercise (−24 ± 9%; 21). Finally, prior high-intensity arm cycling reduces exercise tolerance during leg cycling, and the worsened leg cycling exercise performance is associated with a lower reduction in Q_{tw,pot} (−38 ± 13% vs. −26 ± 10%; 19). This last finding underlines the effect that engaging a higher active muscle mass has on...
modulating fatigue. Even though the upper limbs do not directly contribute to cycling exercise, the higher sensory input from engaging and exhausting a greater volume of skeletal muscle was proposed to limit subsequent cycling performance and constrain performance of the locomotor muscles because the maximum tolerable degree of fatigue the exerciser was willing to endure was reached more rapidly (19). Figure 1 provides a simplified summary of our proposal that the active muscle mass modulates the maximum tolerable symptom of fatigue, and the magnitude of performance fatigability. Specifically, as the active muscle mass increases, the degree of performance fatigability is lower as the sensory input from a larger muscle mass and greater disruption to homeostasis in other physiological systems (e.g. cardiovascular, respiratory) increases; ultimately these adjustments summate to collectively modulate the symptom of fatigue the exerciser experiences.

Rossman et al. (13, 14) acknowledged the task-specificity of performance fatigability, and proposed that a reduction in the exercising muscle mass permits the development of greater performance fatigability because of a reduction in the source of group III/IV afferent feedback to a more local, and less diffuse, signal. Central to this interpretation remains the idea that feedback from group III/IV afferents act to inhibit central motor command to skeletal muscle to restrict the development of performance fatigability to a specific critical level. While conceptually similar, we propose that the higher magnitude of performance fatigability observed after single compared to double leg exercise is not tightly regulated to a task-specific level, but rather is simply a consequence of a greater recruitment and subsequent stress of a greater volume of skeletal muscle. The smaller active muscle mass (both involved and non-involved skeletal muscle), and lower activation of cardiac and respiratory muscle systems.
affords a greater mass-specific blood flow to the exercising muscle (24), and a
progressively greater recruitment of additional muscle fibers (17). This smaller active
muscle mass permits the exerciser to endure greater perturbations to contractile
function as the threat to homeostasis is predominantly restricted to a single muscle
group, and as such a larger magnitude of performance fatigability can be incurred
before the fatigue elicited by the task is perceived as intolerable. As previously
described, it is the symptom of fatigue that is the likely “regulated” variable
determining exercise tolerance, modulated by interactions between the factors that
underpin performance and perceived fatigability.

Performance fatigability and exercise intensity

The active muscle mass engaged during exercise interacts with exercise intensity (and
consequent duration) to determine the magnitude of performance fatigability. Before
any discussion of the importance of exercise intensity in determining performance
fatigability, consideration of the well-established intensity-duration relationship
characteristic of exercise performance is necessary. Briefly, the peak intensity of any
mode of activity declines as the duration of the task increases. The relationship
between intensity and duration can be described by a hyperbolic function with two
key features; i) the intensity asymptote of the intensity-time hyperbola corresponds to
a maximum sustainable intensity (the critical intensity, CI) and ii) the curvature
constant of the hyperbola denotes a finite amount of work that can be performed
above CI, termed $W'$ (25). The CI denotes the boundary between the “heavy” and
“severe” exercise intensity domains. Sustained activity above CI, in the severe
domain, elicits perturbations to intramuscular homeostasis that ultimately result in
task failure. Exercise below CI is theoretically fatigue-free, though in reality this
The prediction is not correct (26). The performance and physiological characteristics of the intensity-duration relationship are critical to consider when discussing any integrated model of fatigue. For the most part, we will discuss data from exercise tasks completed to the limit of tolerance at intensities above the CI.

Within the same exercise mode, the intensity of the task can modulate the level of performance fatigability such that increases in intensity result in greater reductions in $Q_{tw,pot}$ (20, 22). However, the effect of intensity on performance fatigability is negligible when the active muscle mass is small, the intensity is above CI, and the relative demand on other modulators of fatigue is minimized (17). When the active muscle mass is higher, (such as during whole body locomotor exercise), the exercise intensity will influence performance fatigability; higher exercise intensities result in a greater recruitment and subsequent adjustment of the active musculature, and a greater reduction in potentiated twitch. These proposals are explained below.

During locomotor exercise (cycling and running) to volitional exhaustion, the degree of performance fatigability is modulated by exercise intensity. Specifically, data from our laboratory showed the reduction in $Q_{tw,pot}$ is exacerbated with increased exercise intensity (20, 22). For example, during constant-load cycling at relative intensities of 100%, 76% and 64% of $P_{max}$, we observed physiological responses consistent with exercise above CI in the severe domain, and post-exercise reductions in potentiated twitch force of $-33\%$, $-16\%$ and $-11\%$, respectively (20). Additionally, the greatest reductions ($>50\%$) observed in potentiated twitch after cycling exercise have been reported after repeated sprint cycling exercise, which theoretically offers a model where exercise intensity is “all-out” or maximal (15, 16). The same pattern has also
been observed in running exercise; reductions in potentiated twitch after repeated sprint running (−24%; 21) are higher than after 90 min of intermittent exercise (−14%; 27), and after marathon running, where no significant decline in $Q_{tw, pot}$ has been observed (28). In all of these studies there was a short time delay (typically 1-2 min) between the cessation of exercise and the measurement of performance fatigability that could potentially confound comparisons both within- and between-studies (29). However, even with this confound, the magnitude of difference observed both between- and within-studies supports the supposition that locomotor exercise-induced performance fatigability (measured by reductions in $Q_{tw, pot}$) is exacerbated with increasing exercise intensity.

In contrast to whole body cycling exercise, the magnitude of performance fatigability after exhaustive single limb exercise above CI is unvarying (17). Additionally, magnetic resonance spectroscopy studies show a similar post-exercise metabolic derangement after exhaustive single-limb exercise at different intensities above CI (30), although these metabolic responses have previously been dissociated from measurements of performance fatigability (31). Whilst these observations contradict the proposal that exercise intensity can modulate the degree of performance fatigability, they can be explained by the interactive effect of exercising with a small active muscle mass. Specifically, when the active muscle mass is smaller there is a lower demand on maintaining homeostasis in other physiological systems. As such, the exerciser is able to tolerate a higher magnitude of performance fatigability specific to reductions in contractile function before the maximum tolerable symptom of fatigue is attained. The reader is referred back to Figure 1 for a graphical illustration of this concept; during single-limb exercise the stress to other modulating factors is
minimized, such that a greater (perhaps maximum volitional) magnitude of performance fatigability can be attained before the symptom of fatigue becomes intolerable. This premise explains why exercise intensity modulates performance fatigability after exhaustive exercise above CI in locomotor, but not single-limb exercise modes.

**Challenges to the model; afferent blockade.**

Thus far our proposal has been based on correlative evidence, and observations between studies. The strongest challenge to the idea that performance fatigability is task-dependent and not regulated to a critical threshold is provided by experimental studies that used an intrathecal opioid analgesic (fentanyl) to attenuate the activity of group III/IV afferent feedback during exercise. These elegant studies have consistently demonstrated that, when group III/IV afferent feedback is blocked by fentanyl, participants voluntarily incur a higher degree of performance fatigability (8, 9, 32). The subsequent interpretation of these observations emphasize the decisive role that group III/IV feedback from exercising skeletal muscle plays in determining exercise tolerance, via sensory input that mediates central motor command during exercise to constrain the development of performance fatigability to a specific, unvarying, task-dependent level.

Although seemingly in opposition to our proposal, a reinterpretation of the data from these studies provides support to the idea that the magnitude of performance fatigability is dependent on the active muscle mass engaged, and disruption to homeostasis in multiple physiological systems, which collectively combine to modulate the symptom of fatigue and thus determine exercise tolerance. In addition to
attenuating the activity of group III/IV afferents, the administration of fentanyl also compromises the exercise pressor reflex, which results in an attenuation of the cardiopulmonary response to exercise (33). Consequently, the disruption to these physiological systems, and the demand for cardiac and respiratory muscle work, is attenuated, which theoretically reduces their input to modulating the symptom of fatigue (see Figure 4, Amann et al., 2009 (8), and Figure 3, Amann et al., 2011 (9)). We contend this enables the exerciser to recruit and exhaust a greater volume of the knee extensor musculature during the task for the same symptom of fatigue because there is less sensory input from, and/or demand on, the respiratory and cardiovascular systems, not because there is a compromised regulation to a critical threshold. In support of this proposal, the attenuated cardiovascular and respiratory response observed in these studies was concurrent with a greater recruitment of the knee extensor musculature during the cycling bout (see Figure 2, Amann et al., 2009 (8), and Figure 2, Amann et al., 2011, (9)) when group III/IV afferent feedback was blocked. Estimates of muscle activation via surface EMG are subject to a number of valid critiques (34-36), particularly a lack of sensitivity in detecting small differences in exercise intensity. Considering this, it is perhaps particularly striking that participants had a consistently higher surface EMG after fentanyl administration even though they were cycling at the same absolute intensity (9). Figure 2 illustrates this alternative reinterpretation; in panel A, the symptom of fatigue is modulated to a greater extent by adjustments in cardiovascular and respiratory systems, probably mediated primarily by the stress to cardiac and respiratory muscle. This sensory input indirectly limits the adjustments in contractile function by providing a greater contribution to the tolerable fatigue the exerciser is willing to endure. Panel B illustrates how these inputs change when group III/IV afferent feedback is blocked;
the relative input of cardiopulmonary adjustments to modulating fatigue is reduced, which permits the exerciser to stress a greater degree of the locomotor skeletal muscle before the maximum tolerable perception of fatigue is attained. These data also demonstrate that, although skeletal muscle is the ultimate “limiter” of exercise performance, disruption to other physiological systems can modulate the symptom of fatigue even if such disruptions are submaximal relative to the higher capacity of these systems (18).

**Does group III/IV afferent feedback from skeletal muscle contribute to fatigue?**

The activity of group III/IV afferent feedback from exercising skeletal muscle clearly contributes to the optimal regulation of exercise by instigating adjustments in multiple physiological systems in response to the homeostatic threat that exercise might impose (33, 37). Without such feedback, exercise regulation is almost certainly compromised, at least for high-intensity locomotor exercise lasting < 10 min (8, 9, 32). Indeed, Amann et al. (8, 9) clearly demonstrated that when such feedback is blocked participants self-select exercise intensities and/or inappropriate recruitment strategies that result in significant additional performance fatigability in comparison to a control, with no improvement in exercise performance. These data clearly support the idea that group III/IV afferent feedback is important for the regulation of exercise, at least indirectly.

The critical threshold hypothesis proposes that metabolite-mediated, non-nociceptive feedback also acts directly, in a negative feedback loop, on the central nervous system to restrain central motor command to limit reductions in contractile function to a specific level (7). In this review we have argued that adjustments in skeletal muscle as
a consequence of exhaustive exercise are intensity- and mode-dependent, and not
regulated to a critical threshold. Additionally, it is questionable whether non-
ociceptive group III/IV afferent feedback from skeletal muscle has any impact
beyond the appropriate stimulation of the exercise pressor reflex. The potential
modulating role of nociceptive (i.e. pain-related) discharge of group III/IV afferents
on the recovery of muscle force and voluntary activation has been demonstrated using
models of post-exercise circulatory occlusion (38-42), however whether non-
ociceptive afferent act on the CNS is debatable (43-45). In this review we have
conceptualized that disruptions to multiple physiological systems (including skeletal
muscle) combine to modulate the symptom of fatigue via sensory “input”, but the
relative importance of such “inputs” is open to debate. Indeed, the neurophysiological
basis of fatigue, and the extent to which afferent feedback determines endurance
exercise performance remains the subject of fervent debate (44-48). Some theorists
propose the fatigue experienced during exercise is mediated primarily by the
integration of multiple afferent sensory inputs (49), whereas opponents cite the
processing of corollary discharge from premotor/motor areas as the primary factor
mediating the perception of effort experienced during exercise (50). A limitation
within these debates is the concept of the RPE as a measure of fatigue is not described
in detail to afford a valid comparison between studies (51). A detailed discussion is
beyond the scope of the current review. Regardless of whether the fatigue experienced
during exercise can be explained by afferent or efferent mechanisms, understanding
the significance of different adjustments (both physiological and psychological) that
contribute to fatigue, how these vary with the exercise task, and how the tolerance of
fatigue can be modulated by intervention remain key questions for our understanding
of human performance (2).
CONCLUSION

The critical threshold hypothesis proposes that group III/IV afferent feedback from skeletal muscle acts directly on the central nervous system to restrain central motor command and limit performance fatigability to a specific, unvarying level. Here we propose the reduction in skeletal muscle contractile function observed after exercise is task-dependent, and determined primarily by the active muscle mass engaged in the exercise bout, the exercise intensity, and the associated disruption to whole body homeostasis. When the active muscle mass is small, greater reductions in contractile function specific to the exercising muscle can be tolerated before fatigue becomes intolerable as the sensory input is confined to a small muscle mass, and disruptions to other physiological systems are smaller. When the active muscle mass is increased, the demands placed on a larger skeletal muscle mass, and the extra disruption to homeostasis in the physiological systems that support exercise, combine and summate to modulate the symptom of fatigue. Consequently, the tolerable level of fatigue the exerciser is willing to endure is mediated less by adjustments in the involved skeletal muscle, as other adjustments in whole body homeostasis contribute to the perception of fatigue. For locomotor exercise the intensity of the task also modulates the magnitude of performance fatigability, as higher exercise intensities will result in the recruitment and subsequent stress of a greater volume of skeletal muscle. This explains why performance fatigability is: i) exacerbated with greater exercise intensity during locomotor exercise, ii) larger at termination of single-limb exercise than double-limb exercise, and locomotor cycling compared with running exercise, iii) is consistent between trials of the same exercise task, and iv) is altered in conditions of “blocked” afferent feedback when the subsequent force or muscle
activation strategies are also altered. The hypothesis put forth in this review provides a plausible alternative interpretation to the idea of a critical threshold, and further experimental work to test this hypothesis is warranted.
**Figure 1.** Simplified illustration of how the active muscle mass required of the exercise task modulates the symptom of fatigue. In picture A, when a single muscle group is exercised to the limit of tolerance, a strong, local disruption to the small muscle mass involved in the task is the primary contributor to the symptom of fatigue (represented by the thick arrow). In contrast, when the active muscle mass is increased (picture B), the demands placed on i) a larger skeletal muscle mass (both involved and non-involved), and ii) the disruption to homeostasis in other physiological systems (cardiovascular, respiratory), all contribute to modulating the symptom of fatigue (represented by a number of thin arrows). As a consequence, the magnitude of performance fatigability, measured by reductions in the involuntary potentiated twitch response to external stimulation, is reduced in the involved, active musculature as other adjustments combine to modulate the symptom of fatigue.
Figure 2. Simplified schematic to demonstrate how potential modulators of the symptom of fatigue are affected by afferent blockade. The compromised exercise pressor response caused by administration of fentanyl precipitates a reduction in cardiovascular (CV) and respiratory responses to exercise, and the subsequent work of cardiac and respiratory muscle is reduced. The reduction in sensory input from these systems allows the exerciser to incur greater reductions in skeletal muscle contractile function before the maximum tolerable symptom of fatigue, which in healthy individuals is strongly associated with the perception of effort, (represented by the dashed line) is attained.
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