Sarcouncil Journal of Medical Series

ISSN(Online): 2945-3550

Volume- 05| Issue- 03| 2026

Review Article **Received:** 15-02-2026 | **Accepted:** 10-03-2026 | **Published:** 27-03-2026

Review of the Effect of Nmes on Mitochondrial Function and Cytokines": Insights from Mechanistic and Clinical Evidence

***Joshua Labadah*[1] *and Edward Oware*[2]**

[1]*University of Texas at El Paso, Texas, TX, USA*
[2]*Kwame Nkrumah University of Science and Technology, Ghana*.

Abstract: Mitochondrial dysfunction in skeletal muscle underlies the pathophysiology associated with classic hallmarks of aging, metabolic disease, neuromuscular disorders, and physical inactivity. While voluntary exercise remains the single most effective physiological intervention for improving mitochondrial content, efficiency, and adaptability, many patient cohorts are not capable of executing adequate physical activity to produce such adaptations. As such, neuromuscular electrical stimulation (NMES) has appeared on the horizon as a promising exercise mimetic capable of stimulating skeletal muscle under the loss of volitional control. The purpose of this narrative review is to integrate findings from human research and hypothesis-driven basic science investigation to develop a comprehensive framework explaining how NMES affects skeletal muscle mitochondrial function. The thesis of this manuscript is that NMES induces mitochondrial adaptation through two non-mutually exclusive processes. Firstly, muscle contractions stimulated by electric impulses are sufficient to induce metabolic stress to activate canonical muscle signaling pathways, especially those mediated by AMPK and PGC-1α. Secondly, there is nascent evidence to suggest that NMES may stimulate muscle contraction-induced secretion of myokines, which may initiate systemic endocrine signals to modulate mitochondrial function. With this dual mechanism in mind, NMES could move beyond a purely passive approach for atrophy prevention and take on an active role in stimulating metabolism in a way that recreates the essential molecular elements of exercise. Finally, the potential implications of this paradigm for exercise-capacity-limited populations such as those with spinal cord injury, metabolic disease, cancer-associated sarcopenia, or critical illness will be explored in the final section.

Keywords: Neuromuscular Electrical Stimulation (NMES); Mitochondrial Biogenesis; Myokines; Skeletal Muscle; Exercise Mimetic.

INTRODUCTION

Mitochondrial function in skeletal muscle is central to metabolism, exercise performance, and resilience. As the major site of oxidative ATP generation in muscle, mitochondria play key roles in the management of substrate metabolism, redox states, and adaptations during stress conditions. With impaired oxidative function of mitochondria, such as that occurring in metabolic disease, aging, cachexia of cancer, and physical inactivity, muscle efficiency and systemic metabolic function are reduced (Kelley *et al*., 2002). These dysfunctions are more than just biochemical abnormalities and are translated into diminished function and disease.

Exercise has long been proven as an established stimulus in maintaining as well as improving mitochondrial function. Exercise activates various intracellular signaling pathways that result in the augmentation of mitochondrial biogenesis, as well as an increase in the respiratory quotient, due to key regulators such as AMPK, p38 MAPK, as well as the coactivator peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 alpha) (Baar *et al*., 2002; Hood *et al*., 2016). Eventually, these changes result in the augmentation of mitochondrial number, activity, as well as respiratory capacity, thereby improving insulin sensitivity as well as metabolic flexibility (Pesta *et al*., 2011; Groennebaek & Vissing, 2017). However, the fact is that these patients, who can largely benefit from these changes, are unable to participate in voluntary exercise. Neuromuscular injury, severe cardiovascular disease, as well as cachexia due to malignancies, result in a restriction in exercise tolerance as well as adherence, as these patients would not be able to follow conventionally indicated exercise programs (Nash & Gater, 2020).

One further approach that has been identified as a promising alternative method for stimulating skeletal muscle is neuromuscular electrical stimulation (NMES). Through the use of electrical impulses directly on the peripheral nerves or muscle, NMES stimulates muscle contractions independent of neural control, although it also creates a muscle load. Most notably, however, is that the muscle recruitment pattern varies significantly from voluntary muscle contraction, initially recruiting fast-twitch muscle fibers early in muscle contraction (Crameri *et al*., 2002). This is significant because a reversed muscle recruitment pattern is associated with high local metabolic stress, rapid ATP turnover, and early

***Corresponding Author:** Joshua Labadah

DOI- https://doi.org/10.5281/zenodo.19252789

muscle fatigue, all of which have been shown to activate mitochondrial regulatory mechanisms. In subjects who suffer from extreme neuromuscular dissociation and inactivity to the extent of spinal cord injuries (SCI), NMES exercise has been demonstrated to increase the oxidative function of skeletal muscle, mitochondrial enzymatic activity, as well as oxygen consumption (Erickson *et al*., 2017; Ryan *et al*., 2013). Resistance NMES modes have also been demonstrated to increase VO2 peak measurements and mitochondrial respiratory activity in these subjects, suggesting the biological relevance of muscle contractions induced electrically as is generally true in aerobic exercise (Gorgey *et al*., 2021). Despite such improvements, the processes involved in the modulation of mitochondrial health by NMES have not been precisely elucidated. Although previous reviews have focused on specific outcomes such as muscle hypertrophy, fiber transitions, or specific indices of mitochondria, they have not considered the complex cell processes that link the electrically stimulated muscle contraction response to the process of mitochondrial adaptation. In addition, the relationship of muscle contraction to the hormonal role of skeletal muscle has been given scant regard.

Exercise physiology has proven that skeletal muscle is also an active endocrine organ capable of releasing contraction-induced cytokines and peptides collectively denominated myokines, referring specifically to interleukin-6, irisin, and myonectin, among others (Truong *et al*., 2017). These components trigger autocrine, paracrine, and endocrine actions concerning mitochondrial biogenesis, metabolism, and inflammation pathways. Recently, there is emerging evidence that NMES stimulates cytokine responses similar to those during voluntary contraction, suggesting that muscle stimulated by electric contraction might also participate in the regulation of systemic metabolism, aside from the stimulated muscle fibers themselves (Truong *et al*., 2017). The contribution of myokine signaling during NMES-induced mitochondrial adaptability is inadequately understood.

In particular, as a result of these considerations, this narrative review aims to compile peer-reviewed literature on the improvement of mitochondrial function brought about by NMES and exercise-induced cytokines. In other words, through the analysis of evidence emerging from human clinical research and current literature on the role of electrically stimulated muscle activity on mitochondrial function and maintenance, as well as a discussion of the role of contracting-induced cytokines on these processes, the current review aims to propose a two-component conceptual framework based on which the improvement of mitochondrial function brought about by NMES can be viewed as a result of the additive impacts of (i) direct muscle stimulation, on one hand, and (ii) contracting-induced cytokine stimulation brought about by NMES, on the other.

MITOCHONDRIAL BIOLOGY IN SKELETAL MUSCLE

Mitochondria in skeletal muscle cells are very dynamic, with morphology, mass, and function being continually modulated according to metabolic demand. Apart from their traditionally recognized role in ATP supply, mitochondria also regulate lipid, glucose, reactive oxygen species (ROS), and calcium signaling. In the healthy muscle, oxidative phosphorylation is precisely coordinated according to functional demand over a large physiological range. Any mismatch due to lack of exercise, aging, metabolic disorders, or muscle damage leads to decreased respiratory capacity, which defines a dysfunctional muscle (Kelley *et al*., 2002).

One of the most intensely researched adaptive processes in skeletal muscle mitochondria is biogenesis. Contraction triggers increased turnover of ATP and elevated cellular AMP/ATP ratios, activating AMP-activated protein kinase (AMPK), the primary energy sensor in cells. AMPK activates a transcriptional program aimed at mitochondrial growth and metabolism, mainly through the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), which is primarily activated by AMPK (Baar, 2006). PGC-1α mediates the transcriptional program for nuclear-encoded mitochondrial transcripts and activates mitochondrial DNA transcription, firmly establishing PGC-1α as the master transcriptional regulator of the oxidative phenotype. Figure 1 summarizes the principal signaling pathways governing skeletal muscle mitochondrial biogenesis and quality control, highlighting the roles of energetic stress–induced AMPK activation, PGC-1α–mediated transcriptional regulation, and mitochondrial dynamics. Empirical evidence from animal and human studies suggests that upregulation of PGC-1α activity is strongly associated with increased mitochondrial density and oxidative enzyme activity following muscle

Publisher: SARC Publisher

contraction activity (Hood *et al*., 2016). Upstream factors further narrow the response specificity. In addition to AMPK, calcium-mediated and NAD^+-sensitive deacetylases, sirtuin-1 (SIRT1), mediate PGC-1α activity during responses to energy stress, directly associating mitochondrial biogenesis with energy metabolism in cells (Baar *et al*., 2002). Importantly, adaptations of mitochondria are not restricted to their quantitative expansion. It is increasingly recognized that the functional aspect of mitochondria, such as the efficiency of respiration, oxidation of substrates, and coupling of oxidative phosphorylation, might be improved without significant expansion of their volume density. This is particularly the case for endurance and resistance training, in which improvements of the capacity for mitochondrial respiration were observed despite non-significant increases in the mitochondrial content, thus underlining the significance of qualitative adaptations (Pesta *et al*., 2011; Groennebaek & Vissing, 2017). These improvements are a result of coordinated adaptations of the activity of the electron transport chain, substrate uptake, and enzymatic regulation rather than just the expansion of mitochondria. This aspect is of prime importance in the case of the clinical population, for which the restrictions on training volume or intensity might prevent significant increases in mitochondrial content, whereas improvements of their efficiency and function are possible.

Aside from biogenesis and respiration, mitochondrial function requires critical attention to a series of quality-control processes. Mitochondria also exist as a reticular network that operates under cycles of fusion and fission. These cycles ensure rapid distribution of materials inside mitochondria as well as the separation of dysfunctional cellular components. Fission also enables the selective degradation of dysfunctional organelles via mitophagy. On the other hand, fusion helps to preserve the structural integrity of the mitochondrial network and its bioenergetic functions.

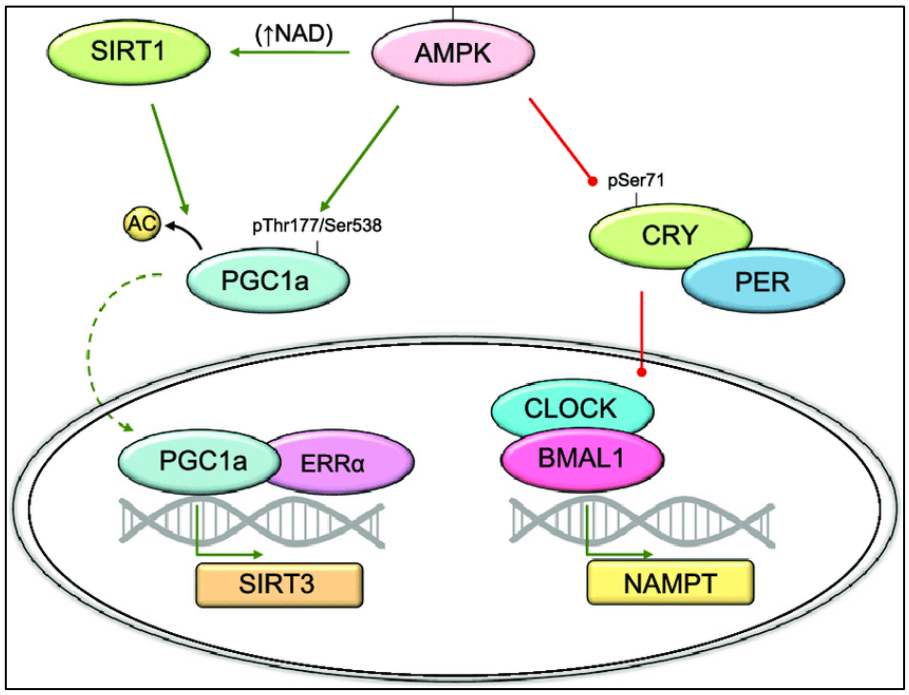

Figure 1. Schematic overview of mitochondrial biogenesis and quality-control mechanisms in skeletal muscle. Muscle contraction–induced energetic stress activates AMP-activated protein kinase (AMPK), promoting PGC-1α–dependent transcription of nuclear and mitochondrial genes involved in oxidative metabolism. Mitochondrial function is further regulated through coordinated fusion–fission dynamics and mitophagy, which collectively maintain mitochondrial efficiency and metabolic adaptability.

The imbalance of these processes, particularly excessive fission and defective mitophagy, can lead to diminished mitochondrial function and oxidative capacity, as well as defective respiration-induced oxidative damage and aging muscle function (López-Lluch, 2017). Muscle contractile function indirectly affects mitochondrial dynamics as a regulatory stimulus under cellular calcium flux and redox conditions. Mitochondrial turnover and renewal counteract the continuous process of

Publisher: SARC Publisher

energetic stimulation. This process maintains the functionally active status of mitochondrial populations. In a current analysis of the literature on interventions focusing on muscle metabolism improvements, attention to the structural integrity of these regulatory mitochondrial processes was pointed out as critical to make interventions more effective (López-Lluch, 2017). These regulatory pathways underscore the pivotal notion of skeletal muscle biology: mitochondrial regulation relies not upon contraction but upon functional needs. The extent, duration, and energy demand of muscle activation dictate the regulation pathways activated. Various contraction patterns of skeletal muscle, such as those with more emphasis upon endurance training and/or resistance training, can activate partially overlapping pathways at the molecular level that target the PGC-1α and related transcription factors, leading to specialized mitochondrial regulation (Pesta *et al*., 2011; Groennebaek & Vissing, 2017). This notion plays a direct role within the context of electrically evoked muscle contractions. In this respect, the neuromuscular electric stimulation (NMES) protocol deviates significantly from voluntary activity due to differences in nervous control and motor unit activation but imposes a considerable energy load upon the activated muscle fibers.

NEUROMUSCULAR ELECTRICAL STIMULATION AS AN EXERCISE MIMETIC

Neuromuscular electrical stimulation (NMES) is a treatment technique in which controlled electrical currents are used to stimulate peripheral nerves or muscles to contract skeletal muscles involuntarily. Unlike voluntary contraction, which relies on the central governing commands from the brain through descending nerve stimulation, NMES does not involve the central nervous system as it stimulates the motor nerve axons through depolarization. The major difference in muscle activation patterns affects mechanical, metabolic, as well as molecular levels in skeletal muscle.

Motor Unit Recruitment and Metabolic Demand

During voluntary contraction, the contraction of motor units usually follows a progressive, or size-related, pattern, which proceeds from low-threshold, fatigue-resistant type I fibers to high-threshold, fast-twitch fibers. On the other hand, NMES follows a spatially fixed, nonselective, and synchronized pattern, which usually affects large, more superficial axons containing fast-twitch fibers (Crameri *et al*., 2002). This reversed pattern of muscle activation further accounts for the early development of fatigue associated with NMES, which places high metabolic demands on the recruited fibers. Consequently, the evoked muscle contractions in the presence of NMES lead to a large, localized ATP turnover, accumulation of by-products of metabolism, and a reliance on oxidative metabolism, even though the magnitude of the evoked muscle forces might be small. This parallels main characteristics of high-intensity muscular exercise and has been shown to stimulate the intracellular signaling pathways responsible for mitochondrial biogenesis.

Cellular Signaling and Overlap Between NMES and Voluntary Exercise

Notwithstanding the differences in muscle unit activation, the downstream cellular phenomena after muscle activation remain identical. Depolarization due to electric muscle activation results in the release of acetylcholine, muscle action potentials, the release of calcium ions from the sarcoplasmic reticulum, as well as cross-bridge cycling between actin and myosin. These actions generate identical tensile stress and metabolic stress as that of voluntary muscle activation. Owing to the identical physiological phenomenon, electrically induced muscle activation recruits identical early anabolic, metabolic pathways as those of voluntary muscle activity. Through experimental evidence, NMES-induced protein phosphorylation of major regulators in the AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways has been proven, highlighting the direct association of electric muscle stimulation with metabolic reformation, protein synthesis, as evident in major studies on NMES (Bickel *et al*., 2003; Osorio-Fuentealba *et al*., 2013). At the transcriptional level, strong evidence identifies NMES as an exercise-mimetic stimulus. In a pivotal in vitro experiment, Son *et al*. (2019) proved that electric muscle stimulation of myotube muscle contractions demonstrated an identical gene upregulation pattern as in in vivo endurance muscle exercise. Interestingly, this similarity covered mitochondrial metabolism, oxidative, as well as muscle remodeling-related gene expressions, providing rigorous direct molecular evidence that electric muscle stimulation could mimic identical events of muscle exercise.

Publisher: SARC Publisher

NMES Training Paradigms and Physiological Specificity

The adaptive response to NMES can be directly impacted by stimulation parameters, which could be varied to target various physiological adaptations. Resistance-type NMES stimulation parameters would involve greater stimulation intensity (to tolerance), greater frequency (50-100 Hz), shorter contraction durations, and greater inter-contraction intervals to maximize muscle hypertrophy and muscle strength (Ryan *et al*., 2013; Gorgey *et al*., 2020). On the other hand, lower frequencies (10-30 Hz), longer stimulation cycles, and greater overall stimulation session times would be utilized in endurance-type NMES stimulation protocols to maximize muscle oxidative capacity (Crameri *et al*., 2002; Erickson *et al*., 2017). These protocol-dependent responses underscore the relevance of dose, interval, and training volume in influencing NMES-induced responses. The heterogeneity among the various studies concerning stimulation parameters, training duration, and intervention period varies considerably, making it difficult to establish consistent standard NMES protocols in targeting the adaptations involving the mitochondria.

NMES as a Practical Exercise Surrogate in Clinical Populations

Clinical trials conducted on human subjects have yielded strong evidence regarding the potential use of NMES as a practical exercise substitute in the context of limited voluntary motor function. Indeed, in the context of spinal cord injury, the repeated use of NMES has yielded improved oxidative function in skeletal muscle, increased oxygen utilization, and the promotion of an oxidative shift in muscle phenotype, which are all typical exercise-induced perturbations (Crameri *et al*. 2002; Ryan *et al*. 2013; Erickson *et al*. 2017). These findings are all the more striking given the intense inactivity and muscle atrophy to which this particular population is prone. Of particular importance, however, is the observation that NMES is considered to be safe when used in the context of proper electrode positioning and stimulation protocols. Mild, temporary adverse events, usually described as discomfort or contact dermatitis, are reported (Toth *et al*. 2020). The feasibility of NMES in severely compromised voluntary motor function, be it complete spinal cord injury, critically-ill patients, or in the case of advanced osteoarthritis or cancer fatigue, represents the potential for NMES to serve not only as the rehabilitation actuator, but a substitute exercise program, capable of administering a controlled physiological stimulus to otherwise inert musculature. Although the immediate responses to NMES are predominantly localized to the muscle being stimulated, there is growing support for the idea that electrically induced muscle contractions may yield systemic responses patterned on those seen in voluntary exercise. NMES has been demonstrated to result in the elevation of circulating cytokine levels, suggesting the possibility that electrically stimulated muscle acts as an endocrine tissue that could modulate metabolism and inflammation both locally and in response to voluntary exercise (Truong *et al*., 2017). It is this idea that leads to the new thinking that NMES-mediated adaptations may be the result of both intramuscular and contraction-mediated cytokine signaling pathways. The resolution of the relative importance of each has both major implications and forms the focus of the latter part of this review.

EFFECTS OF NEUROMUSCULAR ELECTRICAL STIMULATION ON SKELETAL MUSCLE MITOCHONDRIAL FUNCTION

Neuromuscular Electrical Stimulation (NMES) can potentially serve as an exercise substitute only if the electrically stimulated muscle contractions are able to produce biologically significant increments in the mitochondrial function of the skeletal muscle. There are an increasing number of studies on humans that suggest exposure to NMES can produce adaptive responses in mitochondrial bioenergetic, oxidative, and oxygen use capacities of mitochondria in populations that are defined as being extremely physically inactive. These adaptive responses have been shown to go beyond mere structural alterations and involve elements of functional mitochondrial responses.

NMES-Induced Changes in Mitochondrial Oxidative Capacity

A uniform result of NMES interventions is the improvement of the skeletal muscle's oxidative capacity. In subjects with motor-complete spinal cord injury (SCI), using the model of extreme neuromuscular disconnect and disuse, endurance training of NMES has been demonstrated to result in the profound enhancement of skeletal muscle oxidative capacity using near-infrared spectroscopy and other methods of measuring oxygen extraction and utilization with notable accuracy (Mohr *et al*., 1997; Crameri *et al*., 2002; Erickson *et al*., 2017). These experiments have

Publisher: SARC Publisher

confirmed that electrically induced contractions are sufficiently intense to stimulate mitochondrial remodeling even under extreme conditions of disuse. Finally, with regard to whole-body measures of aerobic capacity, the resistance NMES training intervention (NMES-RT) has established improvements. A landmark clinical trial conducted by Gorgey *et al*. in 2021 established that the 12-week intervention of NMES-RT caused significant increases in the peak oxygen uptake rate VO_2 peak in subjects with chronic SCIs. Importantly, improvements within the VO_2 peak were found to be significantly associated with the improved mitochondrial respiration rate in permeabilized skeletal fibers, with emphasis on complex I of the electron transport chains.

Effects on Mitochondrial Enzyme Activity and Bioenergetics

In addition to stimulating oxidative capacity, NMES activates positive alterations in pivotal mitochondrial enzymes and indicators of mitochondrial quantity. In the beginning, experiments by Crameri *et al*. (2002) showed that electrically stimulated leg training produced higher levels of citrate synthase in patients with SCI, providing the first evidence that NMES could stimulate mitochondrial enzymatic potential. Since then, studies have confirmed and extended these findings by employing more comprehensive analyses of mitochondrial bioenergetics. Recently, studies have identified that NMES-RT provokes simultaneous skeletal muscle hypertrophy and mitochondrial function stimulation. Gorgey *et al*. (2024) found simultaneous increases in citrate synthase activity and improvements in the functional ability of mitochondrial complexes I, II, and IV. These findings suggest coordinated stimulation of the mitochondrial enzymatic apparatus, rather than individual alterations. However, it is essential to recognize that NMES-stimulated mitochondrial alterations encompass more than just oxidative enzymes, as NMES has separately been linked to stimulated pathways of glucose metabolism, including enhanced expression of Hexokinase II and improved bioenergetic flexibility (Alharbi *et al*., 2023).

Mitochondrial Respiration, Oxygen Uptake, and Functional Efficiency

The improvement in periphery mitochondrial function during NMES directly leads to an increase in the efficiency of whole-body oxygen utilization. The observed increase in the peak VO_2 during NMES-RT represents a potential increase in the capacity to support an aerobic metabolism with a better coordination of skeletal muscle metabolism and the cardiorespiratory system (Gorgey *et al*., 2021). It is significant that the improvements in the efficiency of ventilation and the utilization of oxygen during NMES-RT in some studies have been noticed without a general increase in the quantity of mitochondrial protein complex which underscores that, the improvement triggered by NMES might be caused not only or not as much by the increase in the quantity of mitochondria as by the improvement in their functional properties or their control ability. The improvement in the efficiency of the respiratory control of the oxidative phosphorylation, as well as in substrate flux, definitely takes a crucial part in this process.

Structural and Molecular Adaptations Supporting Mitochondrial Remodeling

Improved muscle function resulting from NMES has been made possible because of the structural and molecular mechanisms that occur in skeletal muscle. From muscle biopsy studies, it has been observed that NMES training can effectively increase the type I (slow oxidative) and type IIa (fast oxidative) muscle fibers, along with a decrease in type IIx (fast-glycolytic) muscle fibers (Crameri *et al*. 2002; Ryan *et al*. 2013). This muscle fiber changeover enables a muscle environment favorable to the process of oxidative metabolism. On a molecular basis, the process of muscle fiber changeover occurs because of the increased intramuscular signaling mechanisms that regulate mitochondrial biogenesis. Electrically elicited contractile activity has been demonstrated to activate the AMPK pathway along with increased PGC-1α gene expression, as occurs during exercise (Bickel *et al*. 2003; Son *et al*. 2019).

Despite the existence of strong evidence supporting the beneficial effects of NMES on mitochondria, there is interindividual variation in response patterns across different populations and stimulation protocols. The extent of the mitochondrial response also seems to vary according to the underlying muscular and neurological health, as well as the given stimulation protocol itself. Although marked stimulation responses have commonly been found in deconditioned muscle, such as in SCI patients, the ensuing mitochondria stimulation response in other patients might be blunted (Toth *et al*., 2020). Individual differences in stimulation rates, intensities, duty cycles, stimulation session lengths, and cumulative training volumes make it

Publisher: SARC Publisher

challenging to provide a clear comparison of stimulation response patterns across studies, thus contributing to interstudy variation. These findings also confirm the importance of the notion that NMES, while being beneficial in physical exercise, is not an all-purpose alternative to exercise, and its effectiveness is contingent on its similarity to naturally caused muscular contraction in terms of its underlying metabolic needs to activate the mitochondria regulatory mechanism. Overall, the above data support the assertion that the mitochondria of skeletal muscle tissues in people with severe physical inactivity conditions can be stimulated to produce noticeable improvement in their oxidative capabilities, activity of enzymes, respiratory rates, and consumption of oxygen through artificial muscular contraction procedures like NMES

EXERCISE AND NMES-INDUCED CYTOKINES AND MITOCHONDRIAL SIGNALING.

Skeletal muscle is also increasingly viewed as an active endocrine organ that signals through contraction-mediated cytokines and peptides called myokines to remote target tissues. Myokines are proteins produced locally in response to muscle contraction that signal through cytokine pathways; through these pathways, muscle contraction signaling has been expanded beyond the direct and indirect physiological responses involving mechanical work and energetic metabolism. From the mitochondrial biology perspective, myokines offer another signaling pathway by which contraction can regulate mitochondrial biogenesis.

Myokines as Mediators of Exercise-Induced Mitochondrial Adaptation

Among the most investigated exercise-induced myokines is interleukin-6 (IL-6). This cytokine is immediately secreted into the bloodstream in response to muscle contraction. Although IL-6 has long been considered a classical pro-inflammatory cytokine, studies on exercise physiology have revealed it to be a metabolic regulator, stimulating glucose transport, fatty acid oxidation, and mitochondrial biogenesis via mechanisms involving the activation of AMP-activated protein kinase (AMPK). Importantly, IL-6 has autocrine and endocrine actions on skeletal muscles, liver, adipose tissues, and immune cells, thus coordinating the metabolic response to exercise stimulation. Other myokines, irisin and myonectin, are also involved in the regulation of mitochondrial metabolism and function. Irisin, processed by cleavage of the membrane protein FNDC5, has demonstrated the ability to induce mitochondrial biogenesis and oxidative function in muscle and fat tissues, while myonectin is involved in lipid metabolism and mitochondrial substrate handling. These factors, taken together, again emphasize the view that exercise-induced mitochondrial adaptation is no longer a result of local cellular events, with a crucial role played by cooperative endocrine communication.

There is growing evidence supporting a possible role of neuromuscular electrical stimulation (NMES) to trigger cytokine responses similar to those stimulated by voluntary exercise. Muscle contractions induced by electrical stimulation are known to enhance circulating cytokine levels, including IL-6, indicating a possible activation of endocrine-like signaling pathways by NMES-activated muscle fibers even when a motor center is not involved (Truong *et al*., 2017). These findings represent a significant mechanistic development of the exercise-mimetic hypothesis of NMES. There is a biological plausibility for a NMES-mediated myokine release mechanism based on its identical metabolic stress conditions imposed on NMES-activated muscle fibers with regards to ATP turnover, calcium handling, and activation of AMPK signaling pathways (Bickel *et al*., 2003; Osorio Fuentealba *et al*., 2013). All of these conditions are well-identified triggers for myokine release following voluntary exercise. Accordingly, contracted muscle fibers could potentially mimic not only intracellular signaling conditions for mitochondrial remodeling but possibly even extracellular signaling conditions supporting those modifications.

Potential Endocrine Contributions to NMES-Induced Mitochondrial Adaptation

The presence of a potential mitochondrial adaptation mechanism via NMES-induced myokine secretion adds an indirect mechanism by which NMES could act. In this way, myokines secreted from muscle fibers due to electrical stimulation promote an autocrine response that augments mitochondrial signaling within the same muscle, while also promoting paracrine and endocrine responses elsewhere within the body. These systemic responses could then augment overall metabolic regulation within the body and also provide a potential mitigating factor to mitochondrial function within skeletal muscle. While this hypothesis is indirectly supported and intriguing, it suggests that overall metabolic benefits and increased efficiency of oxygen

Publisher: SARC Publisher

consumption within the body following NMES and mitochondrial respiration and oxidative capacity benefits are not solely a local adaptation within muscle (Gorgey *et al*., 2021). Furthermore, that overall glucose and insulin sensitivity benefits exist with NMES, and particularly within a spinal cord-injured population, also suggests a potential role for a systemic metabolic mechanism beyond that of local muscle adaptation (Hjeltnes *et al*., 1998; Alharbi *et al*., 2023). Despite the attractive concept, the role of myokine-induced signaling in the adaptation of mitochondria by NMES remains poorly defined. In contrast to voluntary exercise protocols, there are surprisingly few NMES experiments that include cytokine profiling analyses. Moreover, most trials only used a narrowed panel of cytokines or analyzed a single time-point measurement (Truong *et al*., 2017). Thus, the time-course and dosage effects of myokine expression induced by NMES remain poorly defined.

Moreover, it seems very unlikely that myokine signaling could have a prominent role in terms of being a key driver of mitochondrial adaptation in NMES. Current evidence would suggest instead that cytokine-mediated effects have more of a role in terms of modulatory or amplification mechanisms, which play more of a complementary role in addition to, or instead of, direct intramuscular signaling pathways that are induced through electrically evoked contractions. Such would also appear consistent with current understanding in exercise physiology.

The current literature serves to support a hypothesis based on the NMES-induced mitochondrial response being the result of local and systemic signaling interactions. On the local level, the intramuscular signaling processes, which are associated with the response to the stimulus of mechanical force, calcium, and metabolic stress, initiate the major mitochondrial regulatory pathways involving AMPK, PGC-1α. On a secondary level, the NMES-induced myokine response could enhance these pathways to influence systemic metabolism, thereby producing a physiological environment that contributes to mitochondrial function. The two-pathway model structures NMES, not just as localized muscle therapy, but as a more generalized metabolic activator that has endocrine properties that are, in part, reflective of those found in volitional exercise. The next major step in understanding, or at least optimizing, NMES would be to better understand the role of myokine signaling in these responses.

AN INTEGRATIVE DUAL-MECHANISM MODEL OF NMES-INDUCED MITOCHONDRIAL ADAPTATION

A convergence of the evidence reviewed would indicate that the mitochondrial response of NMES is mediated through more than one mechanism. While purely a localized mechano-stimulation, it would appear that NMES actually simulates the intracellular and systemic processes of voluntary exercise. An integrative dual mechanism would therefore be supported that suggests improvement in skeletal muscle mitochondrial function is mediated through the interaction of intramuscular and endocrine-mediated mechanisms.

Direct Intramuscular Mechanism: Contractile and Metabolic Signaling

The main mechanism by which NMES affects mitochondrial function is mediated by the process of electrically evoked muscle contraction. NMES exerts a high level of energy demand on activated muscle fibers. Despite differences in neural drive, motor unit recruitment, and comparison with conventional exercises, electrically evoked muscle contractions produce similar cellular-level phenomena responsible for mitochondrial adaptation. This intramuscular signaling pathway involves an intracellular calcium-mediated activation of AMPK, calcium-dependent kinases, and intramuscular transcriptional modulators, namely PGC-1α, which regulate mitochondrial biogenesis, electron transport efficiency, and oxidative enzyme gene expression (Baar *et al*., 2002; Baar, 2006; Bickel *et al*., 2003; Son *et al*., 2019). Clinical studies show that NMES enhances mitochondrial oxidative function, respiration efficiency, and enzyme activities, specifically, in individuals with chronic levels of physical inactivity, particularly in individuals with spinal cord injury (Crameri *et al*., 2002; Erickson *et al*., 2017; Gorgey *et al*., 2021, 2024). These studies unequivocally show that NMES is an effective stimulus of canonical exercise-induced intramuscular mitochondrial pathways. Importantly, these NMES-induced intramuscular adaptations also include improvements in mitochondrial quality rather than solely an increase in mitochondrial quantity, which is denoted by improvements in electron transport efficiency, oxygen consumption, and respiration efficiency without a corresponding increase in

Publisher: SARC Publisher

intramuscular mitochondrial protein levels, reflecting a measure of qualitative adaptations (Gorgey *et al*., 2021). This important observation supports that this mechanism is also of high structural and functional relevance.

Indirect Endocrine Mechanism: Myokine-Mediated Systemic Signaling

In addition to local contractile signaling, it appears that NMES might also activate a secondary, indirect signaling system involving cytokines and peptides released by muscle contraction. Voluntary muscle contraction, as well as electrically induced muscle contraction, can trigger cytokine secretion, such as IL-6, a myokine, into the bloodstream (Truong *et al*., 2017). These have an autocrine response on contracting muscles and also affect other tissues, which play a secondary part in regulation, at a distance.

Within this model, NMES-induced myokine release serves as an amplifying and coordinating signal, but not as a primary effector in mitochondrial adaptation. Myokines may serve to augment intramuscular mitochondrial signaling, thereby establishing a body environment that promotes mitochondrial adaptation through modifications in inflammatory, substrate, or insulin-mediated signals. Such a model explains, in turn, improvements in whole-body oxygen uptake efficiency and glucose metabolism outcomes that have been observed with NMES, not only in, but beyond, the NMES-stimulated muscle area, as previously reported by studies in 2021 by Gorgey *et al*. and more recently in 2023 by Alharbi *et al*. More relevant, however, in establishing the physiological role of NMES-related endocrine signals, it would appear, counterintuitive as it seems, that these signals are in fact condition-dependent. While in populations of severely deconditioned subjects, such as those with SCI, it seems probable that even small amounts of whole-body signaling would have large physiologically relevant effects due largely, of course, to the complete lack of competing exercise signals.

Convergence and Feedback between Local and Systemic Pathways

One of the key components of the two mechanisms is how local muscle messages and systemic hormonal signals interact and affect one another. When we activate muscle contractions through an electrical signal, mitochondria adapt because of direct metabolic stress. On one hand, myokines released by muscle tissue could enhance and maintain these adaptations by promoting overall metabolic well-being and shifting away from inflammation. For one, myokines don't eliminate the necessity for direct contraction; they offer a mechanism to sustain mitochondrial well-being.

Understood in this fashion, NMES appears to be something more than simply a mechanical approach to physical rehabilitation. NMES represents a biologically active treatment capable of inducing complex changes within the organism. This, of course, explains just how NMES can enhance mitochondrial function or oxygen-dependent capacities beyond what would otherwise seem feasible given the amount of direct muscle stimulation. Variations in study outcomes can, of course, be largely due to differences in how much of each of these two pathways are turned on.

This dual-mechanism model shifts the understanding of NMES from simply being a method of strengthening muscle tissue to one of actually promoting metabolic adaptation. It provides an explanation for how NMES can be effective for someone with limited exercise ability and suggests how one might calibrate the stimulation protocols for optimal mitochondrial benefits. It seems that protocols emphasizing metabolic stress and myokine production frequency and volume are likely more effective for mitochondrial adaptation than protocols designed for strength. Additionally, combining voluntary exercise protocols with NMES, when feasible, would provide the opportunity for both nervous system-mediated and hormonal-mediated adaptations.

LIMITATIONS AND KNOWLEDGE GAPS

Despite existing research suggesting a meaningful impact of NMES upon skeletal muscle mitochondria, certain necessary parameters and unknowns are currently influencing existing data and future research.

Heterogeneity of NMES Protocols: However, a large obstacle is the variability of NMES protocols between studies. The frequency, pulse duration, intensity, duty cycle, duration of a training session, and total training volume are very disparate between studies (Ryan *et al*., 2013; Erickson *et al*., 2017). So, what kind of muscle fibers will be activated, the intensity of energy metabolism, pattern of fatigue, and post-fatigue response will be very different between studies, making it very difficult to draw comparisons between studies, and

Publisher: SARC Publisher

what could be considered a gold standard of NMES "dose" is, unfortunately, lacking.

Population-Specific Responses & External Validity: A majority of the robust mitochondrial changes associated with NMES have been observed in individuals with very limited activity, especially those with spinal cord injuries) (Crameri *et al*., 2002; Gorgey *et al*., 2021, 2024). While such instances are helpful for analyzing electrically mediated changes, they do not help generalize very well. Pre-existing muscular health, the extent of neuromuscular dysfunction, systemic inflammation, or metabolic health can impact the extent to which the mitochondria are amenable to changes. In more metabolically healthy or ambulatory individuals, the magnitude of change associated with NMES or the associated stimulation protocols could be lesser.

Incomplete characterization of mitochondrial phenotypes: A number of NMES trials use surrogate, often indirect, measures of mitochondrial alterations, such as citrate synthase activity, individual respiratory tests, or whole-body oxygen consumption. Although these tools provide useful information, they do not provide the full perspective. Very few trials have included comprehensive analyses of mitochondrial respiration, coupling efficiency, reactive oxygen consumption, or mitochondrial dynamics/ mitophagy (Pesta *et al*., 2011; Groennebaek & Vissing, 2017). Function may improve without necessarily increasing the quantity, and thus, more precise phenotyping is required to distinguish shifts that are quantitative, qualitative, or produced by different mechanisms.

Poor Understanding of Myokine Signaling Pathways: There now seems to be increasing data that NMES can increase the secretion of contractile-induced cytokines, but there remains a lack of clarity over the relative role of myokine signaling in mitochondrial adaptation (Truong *et al*., 2017). Much of this research has centered on a very small number of cytokines at a single time point, a strategy that fails to elucidate the relative rhythms and dose-response relationships. There is little clarity over the composition and or intensity of the myokine profile induced by the stimulation compared to that of voluntary exercise. A major missing detail relates to the role of myokine as a modulator or driver.

Translational and Implementation Barrierss: From a clinical perspective, implementing NMES as a routine practice also has some challenges, which include access to the device, comfort for patients, supervision required, and ability to comply in the long term. NMES can be considered a relatively safe practice, but higher intensity can be uncomfortable, making it difficult to implement in a situation where maximal metabolic stress is needed. There are very limited studies that can support how long NMES effects on mitochondria last and their influence on clinical outcomes.

FUTURE DIRECTIONS

Future studies will need to focus more upon the design of NMES protocols that are specialized and optimized with the specific intent of impacting mitochondrial measures. A manipulative approach regarding the parameters of frequency, intensity, and duty cycle will be required if comparable doses are to be established. Also needed are longitudinal designs to determine the sustainability of the beneficial effects of NMES upon the mitochondria. A subsequent key step will be the clarification of the endocrine role of myokines. Subsequent trials need to include time-course cytokine analyses as part of the study design since it will serve to clarify if the myokine pathway is a reinforcing or modulating factor within the proposed two-component hypothesis. Finally, it may be possible through the use of voluntary exercise or pharmacologic metabolic modulators to achieve a synergistic effect of enhancing the mitochondrial status of patients or subjects when exercise capacity is limited.

CONCLUSION

This narrative review integrated findings from human studies and mechanistic research on how neuromuscular electrical stimulation (NMES) affects the mitochondrial health of skeletal muscle in people who cannot exercise. The available literature on NMES exercises performed through electrically stimulated muscle contractions makes it possible to speak about the potential effectiveness of this method in increasing the oxidative capacity and efficiency of mitochondrial respiration and metabolism in people who are extremely physically inactive. The article offers a conceptually new interpretation of the available evidence that explains how NMES enhances mitochondrial adaptation through the combination of intramuscular signal transduction initiated by metabolic stress and the potential role of indirect systemic regulation mediated through contraction-

Publisher: SARC Publisher

induced production of myokines. While metabolic stress-induced intramuscular signal transduction seems to represent the main mechanism underlying NMES-induced adaptations, endocrine regulation may potentially enhance and coordinate these effects in certain conditions. The available information generally supports the notion that NMES is more than simply another mechanical rehabilitation method but represents a biologically active exercise-mimetic strategy. Further research on NMES is needed for better use of this approach in persons who are unable to exercise in order to maintain mitochondrial health.

REFERENCES

1. Alharbi, A., Li, J., Womack, E., Farrow, M., & Yarar-Fisher, C. "The effect of lower limb combined neuromuscular electrical stimulation on skeletal muscle signaling for glucose utilization, myofiber distribution, and metabolic function after spinal cord injury." *International journal of environmental research and public health* 20.20 (2023): 6958.
2. Baar, K. "Training for endurance and strength: lessons from cell signaling." *Medicine & Science in Sports & Exercise* 38.11 (2006): 1939-1944.
3. Baar, K., Wende, A. R., Jones, T. E., Marison, M., Nolte, L. A., Chen, M. A. Y., & Holloszy, J. O. "Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1." *The FASEB journal* 16.14 (2002): 1879-1886.
4. Bickel, C. S., Slade, J. M., Haddad, F., Adams, G. R., & Dudley, G. A. "Acute molecular responses of skeletal muscle to resistance exercise in able-bodied and spinal cord-injured subjects." *Journal of Applied Physiology* 94.6 (2003): 2255-2262.
5. Crameri, R. M., Weston, A., Climstein, M., Davis, G. M., & Sutton, J. R. "Effects of electrical stimulation-induced leg training on skeletal muscle adaptability in spinal cord injury." *Scandinavian journal of medicine & science in sports* 12.5 (2002): 316-322.
6. de Smalen, L. M., & Handschin, C. "Mitochondrial Maintenance in Skeletal Muscle." *Cold Spring Harbor perspectives in biology* 17.5 (2025): a041514.
7. Erickson, M. L., Ryan, T. E., Backus, D., & McCully, K. K. "Endurance neuromuscular electrical stimulation training improves skeletal muscle oxidative capacity in individuals with motor-complete spinal cord injury." *Muscle & nerve* 55.5 (2017): 669-675.
8. Gorgey, A. S., Graham, Z. A., Chen, Q., Rivers, J., Adler, R. A., Lesnefsky, E. J., & Cardozo, C. P. "Sixteen weeks of testosterone with or without evoked resistance training on protein expression, fiber hypertrophy and mitochondrial health after spinal cord injury." *Journal of Applied Physiology* 128.6 (2020): 1487-1496.
9. Gorgey, A. S., Khalil, R. E., Carter, W., Rivers, J., Chen, Q., & Lesnefsky, E. J. "Skeletal muscle hypertrophy and enhanced mitochondrial bioenergetics following electrical stimulation exercises in spinal cord injury: a randomized clinical trial." *European Journal of Applied Physiology* 125.4 (2025): 1075-1089.
10. Gorgey, A. S., Lai, R. E., Khalil, R. E., Rivers, J., Cardozo, C., Chen, Q., & Lesnefsky, E. J. "Neuromuscular electrical stimulation resistance training enhances oxygen uptake and ventilatory efficiency independent of mitochondrial complexes after spinal cord injury: a randomized clinical trial." *Journal of Applied Physiology* 131.1 (2021): 265-276.
11. Groennebaek, T., & Vissing, K. "Impact of resistance training on skeletal muscle mitochondrial biogenesis, content, and function." *Frontiers in physiology* 8 (2017): 713.
12. Hjeltnes, N., Galuska, D., Björnholm, M., Aksnes, A. K., Lannem, A., Zierath, J. R., & Wallberg-Henriksson, H. "Exercise-induced overexpression of key regulatory proteins involved in glucose uptake and metabolism in tetraplegic persons: molecular mechanism for improved glucose homeostasis." *The FASEB journal* 12.15 (1998): 1701-1712.
13. Hood, D. A., Tryon, L. D., Carter, H. N., Kim, Y., & Chen, C. C. "Unravelling the mechanisms regulating muscle mitochondrial biogenesis." *Biochemical Journal* 473.15 (2016): 2295-2314.
14. Kang, C., & Li Ji, L. "Role of PGC-1α signaling in skeletal muscle health and disease." *Annals of the New York Academy of Sciences* 1271.1 (2012): 110-117.
15. Kelley, D. E., He, J., Menshikova, E. V., & Ritov, V. B. "Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes." *Diabetes* 51.10 (2002): 2944-2950.
16. Lesnefsky, E. J., Tandler, B. E. R. N. A. R. D., Ye, J. I. A. N., Slabe, T. J., Turkaly, J. U. L. I. A., & Hoppel, C. L. "Myocardial ischemia

Publisher: SARC Publisher

decreases oxidative phosphorylation through cytochrome oxidase in subsarcolemmal mitochondria." *American Journal of Physiology-Heart and Circulatory Physiology* 273.3 (1997): H1544-H1554.
17. López-Lluch, G. "Essential role of mitochondrial dynamics in muscle physiology." (2017).
18. Maruoka, H., Tanaka, K. I., Takayanagi, M., & Zenda, M. "Effects of neuromuscular electrical stimulation on pulmonary alveola and cytokines in chronic obstructive pulmonary disease (COPD) and skeletal muscle atrophy model mice." *Journal of Physical Therapy Science* 33.1 (2021): 1-8.
19. Mohr, T., Andersen, J. L., Biering-Sørensen, F., Galbo, H., Bangsbo, J., Wagner, A., & Kjaer, M. "Long term adaptation to electrically induced cycle training in severe spinal cord injured individuals." *Spinal cord* 35.1 (1997): 1-16.
20. Osorio-Fuentealba, C., Contreras-Ferrat, A. E., Altamirano, F., Espinosa, A., Li, Q., Niu, W., & Jaimovich, E. "Electrical stimuli release ATP to increase GLUT4 translocation and glucose uptake via PI3Kγ-Akt-AS160 in skeletal muscle cells." *Diabetes* 62.5 (2013): 1519-1526.
21. Pesta, D., Hoppel, F., Macek, C., Messner, H., Faulhaber, M., Kobel, C., & Gnaiger, E. "Similar qualitative and quantitative changes of mitochondrial respiration following strength and endurance training in normoxia and hypoxia in sedentary humans." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 301.4 (2011): R1078-R1087.
22. Petro, J. L., Gallo-Villegas, J., & Calderón, J. C. "Myonectin and metabolic health: a systematic review." *Frontiers in Endocrinology* 16 (2025): 1557142.
23. Ryan, T. E., Brizendine, J. T., Backus, D., & McCully, K. K. "Electrically induced resistance training in individuals with motor complete spinal cord injury." *Archives of physical medicine and rehabilitation* 94.11 (2013): 2166-2173.
24. Sanchis-Gomar, F., Lopez-Lopez, S., Romero-Morales, C., Maffulli, N., Lippi, G., & Pareja-Galeano, H. "Neuromuscular electrical stimulation: a new therapeutic option for chronic diseases based on contraction-induced myokine secretion." *Frontiers in physiology* 10 (2019): 1463.
25. Son, Y. H., Lee, S. M., Lee, S. H., Yoon, J. H., Kang, J. S., Yang, Y. R., & Kwon, K. S. "Comparative molecular analysis of endurance exercise in vivo with electrically stimulated in vitro myotube contraction." *Journal of Applied Physiology* 127.6 (2019): 1742-1753.
26. Toth, M. J., Voigt, T. B., Tourville, T. W., Prior, S. M., Guigni, B. A., Schlosberg, A. V., & Dittus, K. "Effect of neuromuscular electrical stimulation on skeletal muscle size and function in patients with breast cancer receiving chemotherapy." *Journal of Applied Physiology* 128.6 (2020): 1654-1665.
27. Truong, A. D., Kho, M. E., Brower, R. G., Feldman, D. R., Colantuoni, E., & Needham, D. M. "Effects of neuromuscular electrical stimulation on cytokines in peripheral blood for healthy participants: a prospective, single-blinded Study." *Clinical Physiology and Functional Imaging* 37.3 (2017): 255-262.
28. Williamson, D. L., Butler, D. C., & Alway, S. E. "AMPK inhibits myoblast differentiation through a PGC-1α-dependent mechanism." *American Journal of Physiology-Endocrinology and Metabolism* 297.2 (2009): E304-E314.
29. Zhu, W., Zhou, Z., Sun, J., & Si, J. "Effects of exercise training on skeletal muscle mitochondrial outcomes in type 2 diabetes: a systematic review and meta-analysis." *Frontiers in Physiology* 16 (2025): 1671926.

Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:
Labadah, J. & Oware, E. "Review of the Effect of Nmes on Mitochondrial Function and Cytokines": Insights from Mechanistic and Clinical Evidence" *Sarcouncil Journal of Medical Series* 5.3 (2026): pp 78-89.

Publisher: SARC Publisher