Skeletal Muscle Damage Produced by Electrically Evoked Muscle Contractions

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FOURÉ, A. and J. GONDIN. Skeletal muscle damage produced by electrically evoked muscle contractions. *Exerc. Sport Sci. Rev.*, Vol. 49, No. 1, pp. 59–65, 2021. *Understanding the physiological/mechanical mechanisms leading to skeletal muscle damage remains one of the challenges in muscle physiology. This review presents the functional, structural, and cellular consequences of electrically evoked submaximal isometric contractions that can elicit severe and localized skeletal muscle damage. Hypotheses related to underlying physiological and mechanical processes involved in severe and localized muscle damage also are discussed. Key Words:* neuromuscular electrical stimulation, muscle activation patterns, skeletal muscle, muscle damage, injury

Key Points

- Electrically evoked submaximal isometric contractions generate unaccustomed muscle activation patterns, which, at long muscle lengths, lead to severe muscle damage.
- Imaging investigations demonstrated a discrepancy between activated and damaged muscle areas after electrically evoked submaximal isometric contractions. Transverse strain and shear stress between active and passive intramuscular structures and between agonist muscles could be involved in severe skeletal muscle damage.
- Minimizing transverse strain within the activated muscles during electrically evoked isometric contractions at short muscle lengths can provide a safe use of neuromuscular electrical stimulation to increase force in athletes and to limit muscle atrophy in patients.

INTRODUCTION

Neuromuscular electrical stimulation (NMES) activates intramuscular nerve branches *via* surface electrodes positioned over a muscle to evoke contractions (1). Although NMES is a method of choice for improving or restoring muscle function in athletes and deconditioned patients (2,3), strong evidence is emerging illustrating that electrically evoked submaximal

isometric contractions can also lead to muscle damage. Strikingly, although the magnitude of active strain has been reported as the main factor of muscle tissue damage after voluntary lengthening contractions (4,5), the underlying mechanisms involved in NMES-induced muscle damage are still unclear.

NMES-evoked submaximal isometric contractions differ from voluntary contractions in their pattern of motor unit recruitment. The neurophysiological differences in motor unit recruitment between electrically evoked and voluntary contractions is beyond the scope of this review, but interested readers are referred to excellent reviews on this topic (6,7). Briefly, NMES induces a temporally synchronous (*i.e.*, imposed by the stimulator) and random activation of both slow and fast motor units even at relatively low force levels (8,9), whereas voluntary contractions induce asynchronous and orderly recruitment. Moreover, muscle areas located beneath and close to the stimulation electrodes are primarily recruited at low stimulation intensity, that is, corresponding to 10%–30% of maximal voluntary contraction (MVC) force (10,11), as illustrated by higher blood flow and oxygen consumption (12), and greater transverse relaxation time (T_2) as measured by magnetic resonance imaging (MRI) (10). Indeed, the greater current density in the vicinity of the stimulation electrodes leads to a preferential depolarization of motoneuronal branches in superficial muscle regions than in the deeper ones (13,14). On that basis, there is now a consensus that the increase in stimulation intensity results in the depolarization of new and deeper motor units (12–14), at least when NMES is applied over the muscle belly (15). This progressive recruitment of motor units from superficial to deep muscle regions leads to inhomogeneous intramuscular activation patterns during NMES, whereas more homogeneous muscle activation and metabolic activity occur during voluntary contractions (12,16). Although deep muscle fibers could be activated at higher electrically evoked force levels until 75% MVC in

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some subjects (17), it remains rare to activate *quadriceps femoris* muscles to a force level higher than 55% MVC, and extremely rare to reach a force level higher than 70% MVC (18,19). Finally, although the four muscles of the *quadriceps femoris* are recruited during voluntary isometric contractions (16), intermuscle activation was heterogeneous during NMES because the *vastus intermedius* (VI) muscle located far from the stimulation electrodes was poorly activated (*i.e.*, T_2 values were 33.1 ± 0.7 and 33.9 ± 0.9 ms before and immediately after NMES, respectively) as compared with the two muscles located in direct contact with the electrodes (*i.e.*, *vastus lateralis* [VL] and *vastus medialis* [VM], for which T_2 values significantly increased from 32.6 ± 0.7 to 37.0 ± 1.9 ms and from 32.9 ± 0.5 to 36.6 ± 2.3 ms, respectively) (10,20).

The specific motor unit recruitment associated with NMES applied over the muscle belly and the related inhomogeneous intra- and intermuscle activation patterns could drive tissue damage (21). This has been clearly demonstrated by the larger changes in indirect outcomes of muscle damage after NMES as compared with those occurring after either submaximal (22)

or maximal voluntary isometric contractions (23). NMES may indeed result in unaccustomed stress and strain among structures within stimulated muscles (24) and potentially between agonists that could be further exacerbated at long muscle lengths. On the basis of the force recovery after the NMES session, it has been reported that electrically evoked submaximal isometric contractions performed at long muscle lengths (*i.e.*, defined as a joint position higher than 70% of the maximal range of motion [RoM_{max}]) (Fig. 1) actually induced severe damage (10,21), whereas no or minor changes in force were reported after NMES at short muscle lengths (*i.e.*, defined as a joint position lower than 50% RoM_{max}) (Fig. 1) (28). However, our understanding of the physiological and mechanical processes involved in the severe damaging effects of NMES-evoked submaximal isometric contractions remains unclear.

This review focuses on recent findings of the functional, structural, and cellular changes resulting from electrically evoked submaximal isometric contractions over a muscle belly. We also provide hypotheses on the potential underlying mechanisms of severe and localized damage at long muscle lengths.

Figure 1. Human studies that have determined effects of a single session of electrically evoked submaximal isometric contractions (NMES session) at long and short muscle lengths defined as the joint angle corresponding to a position higher than 70% and lower than 50% of the maximal range of motion (RoM_{max}), respectively. RoM_{max} (*i.e.*, $\theta_{max} - \theta_{min}$) was determined from previous studies (25–27) for knee extensors (140° [$\theta_{min} = 0^\circ$; $\theta_{max} = 140^\circ$] with 0° : knee fully extended), elbow flexors (140° [$\theta_{min} = 40^\circ$; $\theta_{max} = 180^\circ$] with 180° : elbow fully extended), and plantar flexors (70° [$\theta_{min} = 40^\circ$; $\theta_{max} = 110^\circ$] with 90° : foot perpendicular to the tibia, and lower values represent plantar flexion angles). The joint angle used during the NMES session (θ_{NMES}) was normalized to the RoM_{max} as $\%RoM_{max} = ((\theta_{NMES} - \theta_{min}) / RoM_{max} \times 100)$. For instance, when $\theta_{NMES} = 50^\circ$ for the knee extensors (28), $\%RoM_{max} = 35.7\%$ (*i.e.*, $((50^\circ - 0^\circ) / 140^\circ \times 100)$; when $\theta_{NMES} = 160^\circ$ for the elbow flexors (23), $\%RoM_{max} = 85.7\%$ (*i.e.*, $((160^\circ - 40^\circ) / 140^\circ \times 100)$). Experimental conditions (A–E), changes in maximal voluntary isometric contraction (MVC) force (F), evoked force during the NMES session (G), changes in CK activity (H), and the delayed-onset muscle soreness assessed from the visual analog scale (VAS) (I) were reported. EF, elbow flexors; KE, knee extensors; PF, plantar flexors. **Values estimated from graph, [§]last day of measurement; boxed: peak day from day 1 (D1) to day 4 (D4) after the NMES session.

FUNCTIONAL ALTERATIONS OF NMES-EVOKED SUBMAXIMAL ISOMETRIC CONTRACTIONS AND CHANGES IN INDIRECT OUTCOMES OF MUSCLE DAMAGE

NMES-induced muscle damage was often assessed from indirect markers, such as decreased MVC force, blood sampling parameters (e.g., creatine kinase [CK] activity) and delayed-onset muscle soreness (10,22,23,28–33).

The impact of NMES on indirect markers of muscle damage has been typically investigated by using a low number of evoked contractions (<50 contractions; Fig. 1A) and submaximal intensity (<35% MVC; Fig. 1G). Electrically evoked force levels varied among subjects (as illustrated by the standard deviation in Fig. 1G), likely due to anatomical specificities (e.g., morphological organization of the axonal branches within the muscle) (7) or interindividual differences in current tolerance. The other stimulation parameters were similar among studies, with a pulse duration ranging from 250 to 400 μ s and a stimulation frequency between 60 and 100 Hz (Figs. 1C, D). Duty cycle was usually lower than 40%, although higher values were reported in studies including a large number of contractions (Fig. 1E).

Electrically evoked submaximal isometric muscle contractions led to a large and long-lasting decrease in MVC force when delivered at long muscle lengths (Figs. 1B, F). For instance, 4 d after the NMES session, knee extensor MVC force was reduced by approximately 20% (20,22) and was still reduced by 20% and 12%, even after 7 and 14 d of recovery, respectively (10). Such slow recovery of MVC force at long muscle lengths (i.e., >1 wk; Fig. 1F) is considered as an index of severe muscle damage (34). Interestingly, after a single session of NMES performed at short muscle lengths, changes in MVC force were small, and near full MVC recovery occurred after 2 d (Fig. 1F). In addition, maximal voluntary isometric contractions resulted in smaller changes in MVC force and faster recovery as compared with NMES performed at long muscle lengths (23). These findings clearly illustrated a muscle length dependence of NMES-induced muscle damage and that NMES at long muscle lengths resulted in more damage than voluntary isometric contractions (22,23).

NMES-evoked submaximal isometric contractions at long muscle lengths have been linked to a 10- to 30-fold increase in CK activity (Fig. 1H), further confirming the deleterious effects leading to the leak of cellular elements into the blood stream and illustrating the occurrence of muscle damage. On the contrary, CK activity was moderately increased when NMES was performed at short muscle lengths (Fig. 1H) and remained unchanged after submaximal voluntary isometric contractions (23). It also should be pointed out that high interindividual variability in CK changes can lead to a misinterpretation of muscle damage magnitude, as illustrated by the high-responder phenomenon associated with an exacerbated leakage in the bloodstream (35). As previously reported (36), CK activity should be used in combination with other indirect markers (especially MVC force in humans) to get a clear picture of both the occurrence and the magnitude of muscle damage.

Finally, muscle soreness was abundantly reported in the context of muscle damage but remained subjective and correlated with only a few other indirect markers (37). Muscle soreness usually peaked at 2 d and was greater when NMES was delivered at long muscle than at short muscle lengths (Fig. 1I). In

the same way, soreness was also higher after NMES in comparison with what was found after protocols involving either submaximal (22) or maximal voluntary isometric contractions (23).

Overall, despite submaximal force levels, NMES-evoked isometric contractions at long muscle lengths lead to severe muscle damage. Although the long-lasting MVC reductions can be related to impairments of the central nervous system (37), imaging techniques and muscle tissues analysis are consistent with widespread structural and cellular damage.

STRUCTURAL AND CELLULAR ALTERATIONS RESULTING FROM NMES-EVOKED SUBMAXIMAL ISOMETRIC CONTRACTIONS

Changes in Muscle Structure

The most often reported structural change after NMES-evoked submaximal isometric contractions was a 5% increase in *quadriceps femoris* muscle volume after 4 d, as assessed by MRI (10,20,32,37). More specifically, the largest volume increases were observed in the VM and VL muscles, located beneath and close to the stimulation electrodes. Muscle swelling after a damaging exercise has been related to edema subsequent to tissue damage and inflammation processes (38). This increased intramuscular water volume generated changes in muscle T_2 . In addition, a long-lasting T_2 increase was reported in the VL muscle 21 d after the NMES session (10). In agreement with the minor changes in MVC force, such MRI parameters were not significantly affected when NMES was performed at short muscle lengths (28).

More specific to muscle microstructure assessment, diffusion tensor imaging changes related to intramuscular water diffusion within the tissue have been detected after NMES-induced muscle damage. Increased radial diffusion of water molecules within the directly stimulated muscle was reported, providing indirect evidence of damage to cellular barriers (20,39). These macroscopic changes assessed by MRI were further confirmed by histological analyses from muscle biopsies obtained after the NMES session.

Cellular, Metabolic, and Biochemical Alterations

Only a few studies have directly assessed the cellular alterations resulting from NMES-evoked submaximal isometric contractions at long muscle lengths, and these were done in plantar flexor muscles (29,40). Histological analyses clearly showed disrupted z-lines, the presence of desmin-negative muscle fibers, and the infiltration of macrophages (29), indicating damage at the myofiber and sarcomere levels (elegantly shown in Figs. 3 and 4 in Mackey *et al.* (29)). In addition, a single bout of isometric NMES resulted in a high satellite cell content, significant increases in types I and III collagens, tenascin C immunoreactivity, Ki67⁺ cell number, and gene upregulation for heat shock proteins (i.e., HSP27 and HSP70) and monocyte chemoattractant protein-1 (40), indicating an ongoing muscle repair process after NMES-induced muscle damage.

NMES-evoked submaximal isometric contractions at long muscle lengths also caused a prolonged resting cellular acidosis as measured by ³¹P magnetic resonance spectroscopy (41), illustrating an alteration of resting intracellular pH homeostasis. From a physiological point of view, the resting intramuscular acidosis in skeletal muscle relies on the balance between proton accumulation and removal mediated by transporters located at the sarcolemma. NMES-evoked submaximal isometric contractions

could generate severe damage to sarcolemma, leading to the dysregulation of pH through the impaired activity of the Na^+/H^+ exchangers (42). Interestingly, sodium accumulation in damaged muscle has been recently described in a case study (39). Impaired mitochondrial function, illustrated by a slower PCr recovery rate and significantly decreased total rate of adenosine triphosphate (ATP) production during a standardized rest-exercise-recovery protocol, has also been reported (41). Overall, NMES-evoked submaximal isometric contractions at long muscle lengths largely disturb skeletal muscle fiber homeostasis at rest, as illustrated by decreased pH and an increased sodium concentration. However, the mechanisms leading to the specific structural and cellular alterations induced by electrically evoked submaximal isometric contractions at long muscle lengths are still unclear.

UNDERLYING MECHANISMS POTENTIALLY INVOLVED IN SEVERE SKELETAL MUSCLE DAMAGE

Electrically evoked submaximal isometric contractions generate unaccustomed muscle activation patterns that lead to severe muscle damage at long muscle lengths. In the following sections, hypotheses related to underlying physiological and mechanical processes involved in severe and localized muscle damage are discussed.

The Potential Role of Mechanical Factors

One of the most striking findings after NMES-evoked submaximal isometric contractions reported in a recent study (10) was the discrepancies between the superficial activation and deep damage of the VL muscle. As displayed in Figure 2A, T_2 was significantly increased immediately after the NMES session (*i.e.*, illustrating muscle activation) in the whole VL and VM muscles. However, this activation was significantly higher in the superficial part, especially near the position of the stimulation electrodes (*i.e.*, $+17 \pm 5\%$ in the proximal part for the VL and $+14 \pm 7\%$ in the distal part for the VM), confirming an inhomogeneous intramuscle activation pattern. In addition, little

activation was detected in deep agonist muscle (*i.e.*, VI), suggesting an inhomogeneous intermuscle activation pattern in comparison with what has been observed during voluntary isometric knee extensions (16).

Astonishingly, the damaged muscle areas assessed on the basis of increased T_2 values in the days after NMES session (*i.e.*, day 4 until day 21) were mainly identified in the deep part of the VL (Fig. 2B). The accurate statistical localization of activation and damage after electrically evoked submaximal isometric contractions at long muscle lengths shed light on an interesting phenomenon of localized damage in the deep VL muscle tissue, which also is the less activated muscle area during the NMES session.

The mechanical behavior of both active and passive structures is likely to be a key factor involved in localized muscle damage, but its contribution has been scarcely investigated. To the best of our knowledge, only one study reported changes in muscle architecture during NMES-evoked submaximal isometric contractions of the tibialis anterior (24). Interestingly, shorter fascicle length and higher pennation angle were reported during NMES-evoked submaximal isometric contractions in comparison with torque-matched voluntary isometric contractions. This potential localized contractile activity under the stimulation electrodes could generate unaccustomed strain within activated muscle and interactions with neighboring agonist muscles. Overall, the musculotendinous behavior during NMES-evoked submaximal isometric contractions remains to be more deeply assessed using real-time imaging methods.

During contraction, muscle fiber shortens, leading to tension in both longitudinal and transverse directions (*i.e.*, parallel and perpendicular to the fiber's line of action), as previously reported during electrically evoked contraction of frog single intact muscle fibers (43). One could, therefore, assume that the high transverse tension occurring in the most activated superficial muscle areas (10) could result in a large transverse strain of the deep muscle regions, which were less activated. Considering that passive/

Figure 2. Results of statistical parametric mapping analyses on the thigh muscle T_2 maps between baseline (PRE) and acquisitions performed immediately after (POST) the neuromuscular electrical stimulation (NMES) session related to activation areas (A), and 7 d (D7), 14 d (D14), and 21 d (D21) after the electrically evoked isometric contractions, related to muscle damage (B). The color scale (from red to yellow) represents the degree of significance (low to high). Results of the statistical analysis displayed on two slices (*i.e.*, a distal and a proximal slice represented by thick bars on the sagittal slice on the left) were overlaid on the anatomical axial images. (Reprinted from (10). Copyright © Alexandre Fouré. Used with permission.)

less-active muscle fibers are more prone to be stretched (*i.e.*, because of their low stiffness) than active ones, this transverse strain could exceed the elastic limit of the former, thereby resulting in preferential deep muscle damage (Fig. 3A). Therefore, the transverse strain could be involved in specific damage of costameres within deep muscle fibers. This phenomenon could be further exacerbated at long muscle lengths when the passive tension in the muscle-tendon unit is increased, as illustrated by the lack of damage in stimulated muscles at short muscle lengths (28).

The viscous properties of muscle tissues could also generate inhomogeneous strain along muscle fascicles so that the rate of force production would be slower in the deep passive (or less active) muscle regions as compared with the superficial activated areas (Fig. 3B). Indeed, considering that the rate of muscle force production is high during an electrically evoked tetanic contraction (44), the contribution of the viscous muscle component could lead to inhomogeneous strain velocity along fascicles from superficial to deep regions.

The mechanical behavior of neighboring agonist muscles could also contribute to the transverse strain of the directly stimulated muscle. Indeed, the passive mechanical behavior of the poorly activated VI agonist muscle could increase the transverse strain in the deep part of the VL muscle (Fig. 3C). The relative displacement of these two muscles during NMES-evoked submaximal isometric contractions could create a stress between the corresponding muscle fascias, leading to potential transverse force transmission (45–48). These phenomena could contribute to an increased shear strain on the intramuscular connective tissues that can result in damage, as illustrated by the extracellular

matrix deadhesion after NMES-evoked submaximal isometric contractions (40), particularly at long muscle lengths (28). This hypothesis is further supported by the anatomical features of these two muscles, which display fused aponeuroses in their proximal part (49).

Finally, considering the heterogeneous activation within muscles located directly beneath the stimulation electrodes and the resulting lower muscle activity in agonist muscles during the NMES-evoked submaximal isometric contractions (10), an unaccustomed and nonuniform spatial distribution of stress and strain could also occur within the common tendon (46,47). This potential mechanism was highlighted during isometric voluntary contraction and passive joint motion (46). One could assume that the inhomogeneous intermuscular activation and then the lower activation of agonist muscles during isometric NMES would result in a smaller change in tendon length, thereby inducing a higher strain of passive and distal intramuscular structures (Fig. 3D).

It also should be pointed out that the assumptions of the peculiar behavior and interaction with the surrounding structures are muscle specific. Indeed, MRI observations on the VM muscle clearly showed that activated (Fig. 2A) and damaged (Fig. 2B) muscle areas were mainly superficial. As previously hypothesized (20), this muscle-specific localization of NMES-induced muscle damage could be related to anatomical specificities (*e.g.*, changes in muscle architecture during NMES, interactions with neighboring muscles).

Overall, hypotheses of shear stress within active muscle and among agonist muscles, as well as transversal strain of muscle

Figure 3. Conceptual figure illustrating how electrically evoked submaximal isometric contractions at long muscle lengths may lead to deep localized severe vastus lateralis (VL) muscle damage (10). Several potential mechanisms are described such as the transversal tension (leading to transverse strain on the less activated muscle fibers) (A), the heterogeneous activation from the superficial to the deep part along the muscle fascicle (leading to an inhomogeneous strain velocity along the fascicles related to the viscous properties of skeletal muscle tissues) (B), the passive neighboring behavior of the vastus intermedius (VI) agonist muscle (leading to unaccustomed transverse strain on the VL) (C), and the unaccustomed spatial stress distribution on *quadriceps femoris* distal tendon (leading to shear stress between the deep and superficial regions inside the VL and between the VL and the VI) (D).

structures remain to be carefully assessed during NMES-evoked submaximal isometric contractions. There is no doubt that ultrasound (*i.e.*, B-mode and shear wave elastography) and MRI techniques would be of utmost interest to assess the peculiar behavior of skeletal muscle (24,50) related to severe damage generated by NMES-evoked submaximal isometric contractions, as reported after maximal voluntary lengthening contractions (51).

The Potential Role of Ion Disturbances

The specific recruitment of motor units with NMES can induce greater muscle fatigue to the recruited muscle fibers than voluntary contractions and imposes greater mechanical stress to muscle fibers and the extracellular matrix. It has been suggested that ATP availability can decrease with repeated contractions of the same muscle fibers, eventually resulting in elevated intramuscular calcium ion concentration and activation of phospholipase and protease activities, as reported after maximal voluntary lengthening contractions (21). Considering that MRI and spectroscopy assessments of NMES-evoked submaximal isometric contractions mainly found superficial changes in T_2 and energetic metabolism activity (10,11), it seems unlikely that the deep damage in the VL muscle (10,32) could have been related to a decreased ATP availability in damaged tissues.

Although the role of the calcium-calpain pathway in voluntary lengthening contraction-induced muscle damage has been widely documented (at least in animals; see review of Allen *et al.* (52)), there is, so far, no information on its potential contribution to the severe muscle damage resulting from NMES-evoked isometric submaximal contractions. Moreover, an increased intracellular sodium concentration was reported in a clinical case after NMES-evoked submaximal isometric contractions (39), which could explain the changes in pH homeostasis (41). Further studies are needed to determine whether, and to what extent, intracellular calcium/sodium accumulation plays a role in the severity of muscle tissue damage.

Modulation of Muscle Damage Severity

As previously illustrated in this review, the magnitude of muscle damage can be easily minimized by changing the length of muscle-tendon unit during NMES-evoked submaximal isometric contractions (28). The initial length of the stimulated muscle (*i.e.*, expressed as a percentage of the RoM_{max}) has a major influence on the occurrence and extent of muscle damage. Therefore, it seems that changing the muscle length from 70% to 50% RoM_{max} appears as a relevant strategy for avoiding/minimizing muscle damage (28). This could provide practical recommendations for the safer use of NMES to increase force in athletes and limit muscle atrophy in patients. However, it is likely that there is a threshold from which muscle damage can occur as a result of electrically evoked submaximal isometric contractions, probably due to passive longitudinal and transverse tension levels according to the initial muscle length. Further studies are, therefore, warranted to determine the occurrence and magnitude when the joint angle is progressively increased from 50% to 70% RoM_{max} .

In addition, alterations in the placement and size of the stimulation electrode may influence the severity of muscle damage. Indeed, variability in NMES-associated muscle activation patterns has been reported among T_2 MRI studies (10,17). More recently, growing evidence is emerging on the relevance of

spatially distributed sequential NMES protocols to induce more homogeneous muscle activation patterns (53) and, therefore, limit local intramuscular stress and strain. However, it is still unclear whether such strategies are effective for minimizing NMES-induced muscle damage at long muscle lengths.

Finally, considering the potential contribution of intramuscular shear stress and transversal overstrain of passive structures to NMES-induced severe muscle damage, several strategies of preconditioning could be considered. A significant positive correlation was recently reported between the passive muscle shear modulus and the relative decrease in MVC after damaging exercise (54). Therefore, preconditioning acute and chronic exercises aimed at decreasing muscle passive stiffness could have positive effects on NMES-induced muscle damage. For instance, chronic stretching-induced decreases in muscle and musculoarticular stiffness (55,56) could reduce stress within the muscle during NMES-evoked submaximal isometric contractions and thereby alleviate NMES-induced muscle damage outcomes (57).

CONCLUSION

Electrically evoked submaximal isometric contractions generate unaccustomed muscle activation patterns that, at long muscle lengths, can produce unaccustomed transverse strain leading to severe and localized muscle damage. Interestingly, the modulation of muscle length is a very promising strategy to minimize the potential deleterious effects of NMES-evoked submaximal isometric contractions.

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