Supplemental Materials for

NMJ DISORDERS EXPOSED!

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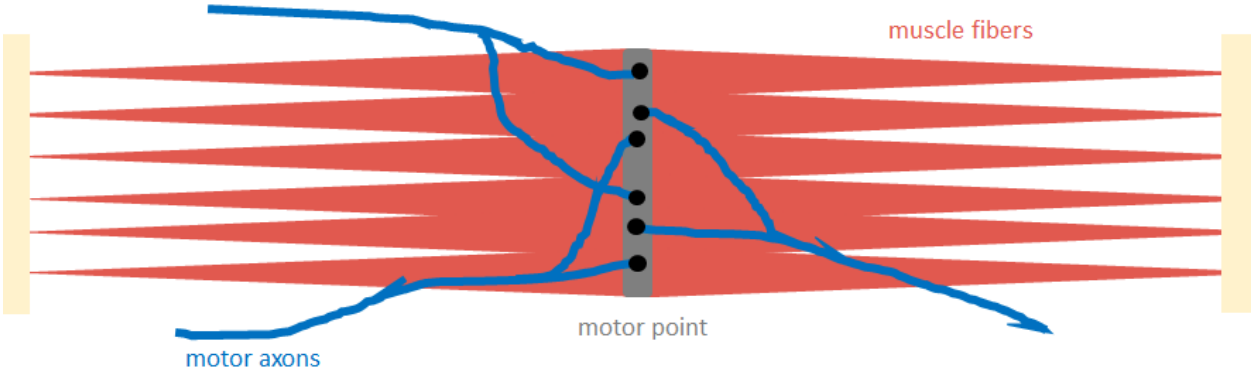
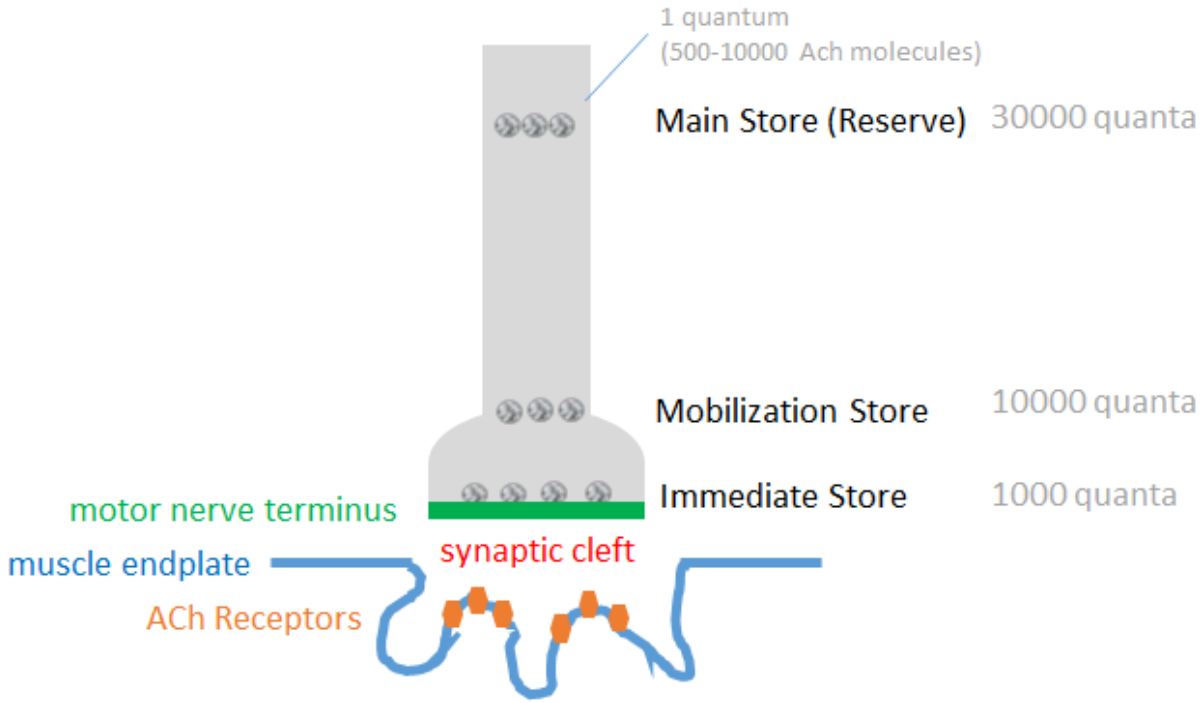
Neuromuscular Junction Physiology

The Neuromuscular Junction At Rest

Each muscle fiber has an endplate, site of the neuromuscular junction.
Within a muscle, the endplates are aligned at the motor point.



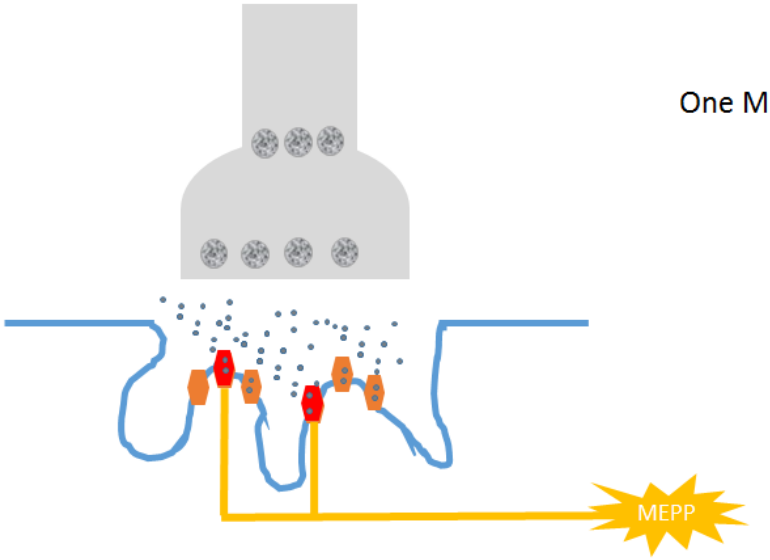
Taking a closer look, the neuromuscular junction itself consists of the motor nerve terminus, the synaptic cleft, and the muscle endplate.



At the neuromuscular junction, a nerve action potential is translated to a muscle fiber action potential, by way of a chemically mediated synapse. The chemical neurotransmitter is acetylcholine (ACh).

Acetylcholine is packaged in vesicles. The amount of acetylcholine contained in one vesicle is a quantum. The quanta are located at three different sites: the immediate store, the mobilization store, and the main store.

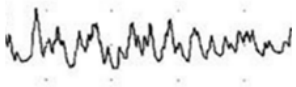
At baseline, there is spontaneous release of acetylcholine into the synaptic cleft. The acetylcholine molecules bind to acetylcholine receptors on the muscle endplate, generating small, non-propagating electrical signals from the muscle endplate. These signals are **miniature endplate potentials (MEPPs)**. The electrophysiologic correlate is endplate noise.



One MEPP = electrical response to 1 quantum of ACh

MEPPs = endplate noise

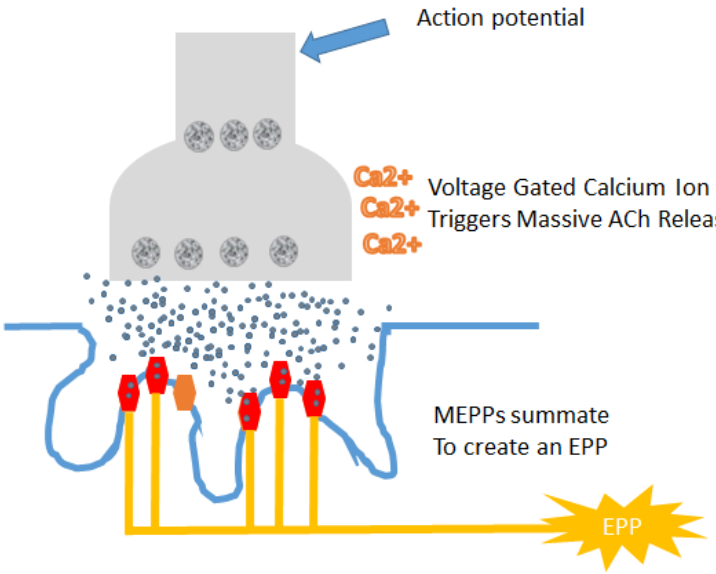
Seashell sound
~50uV amplitude
~20-40 Hz frequency



(Endplate noise image from Preston and Shapiro 2012)

The Neuromuscular Junction with Stimulation

Either nerve stimulation (in the EMG lab) or volitional activation can result in a propagating nerve impulse that reaches the motor nerve terminus. This stimulus triggers massive calcium influx into the nerve terminus via voltage gated calcium channels. The calcium triggers docking of large numbers of acetylcholine vesicles and the release of their contents into the synaptic cleft. The binding of massive amounts of acetylcholine to the receptors leads to generation of an endplate potential (EPP).



If the EPP magnitude reaches threshold for muscle fiber depolarization, sodium channels open, generating an action potential that propagates through the muscle fiber. This **muscle fiber action potential (MFAP)** can be recorded on needle EMG (e.g. endplate spike).

(Downstream of this sequence, excitation-contraction coupling translates this electrical signal into muscle contraction.)

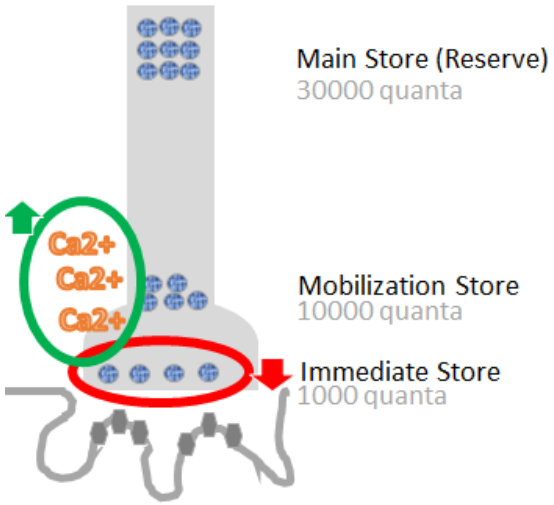
A **compound muscle action potential (CMAP),** as recorded during nerve conduction studies, represents the summation of MFAPs over the recordable area of the muscle. Thus, a CMAP is a graded response, whose magnitude is based on how many MFAPs fire.

Repetitive Stimulation: In Normal and Diseased States

Repetitive Nerve Stimulation in the Normal State

Repetitive stimulation can exert opposing effects on acetylcholine release at the neuromuscular junction:

depletes ACh stores (over time)	brings in calcium (brief, 200 ms)
↓ EPP	↑ EPP



The dominant effect on the CMAP during nerve conduction studies with repetitive **stimulation depends on the rate of stimulation**. At **slow rates of stimulation**, the calcium influx dissipates fully between successive stimulations, such that there is no significant accumulation of calcium. Thus, the effect of the repetitive stimulation is depletion of acetylcholine stores, diminishing the resultant EPPs.

However, **at fast rates of stimulation (greater than 10 Hz),** calcium accumulates in the nerve terminus with each successive nerve action potential. Increased calcium driving increase acetylcholine release becomes the dominant effect, driving up the resultant EPPs.

To summarize:

Slow RNS (2-3 Hz)	favors depletion of immediate ACh stores

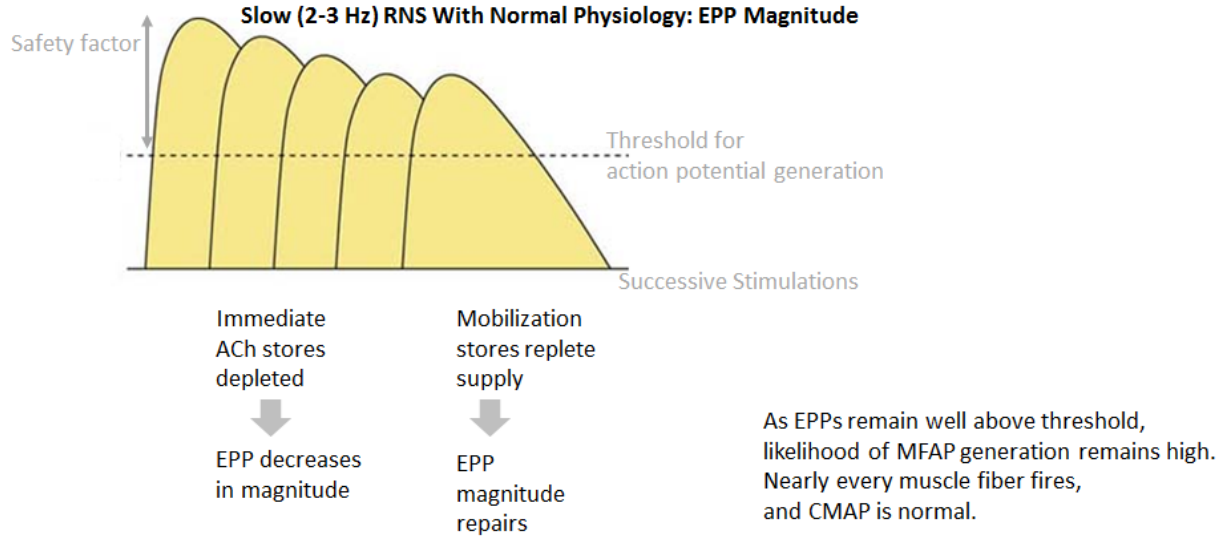
Furthermore:

Post-exercise exhaustion (max exercise x 1 minute)	furthers this depletion effect by further depleting stores

In contrast:

Rapid RNS or Brief Maximal Exercise (10 sec)	favors potentiation with calcium accumulation

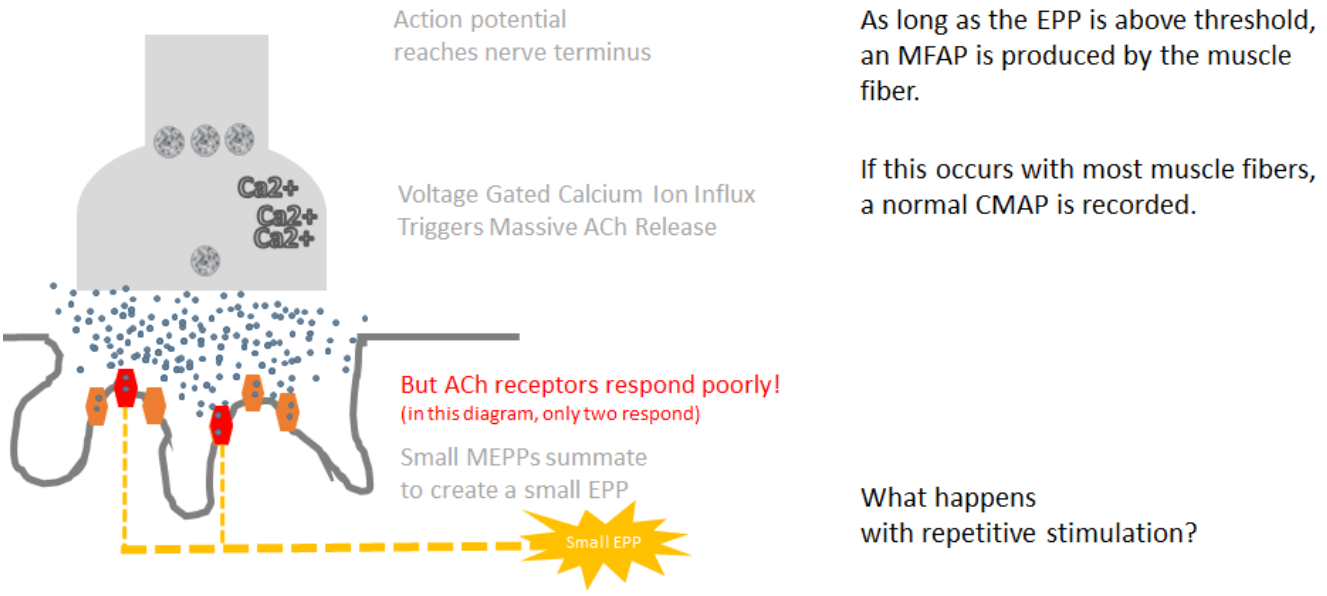
However, in the absence of pathology, these conditions do not result in significant changes to the recorded CMAP. Although they alter EPP magnitude, the EPP magnitude far exceeds the threshold for action potential generation (this gap is the **safety factor**), such that these alterations do not result in decreased MFAP generation.



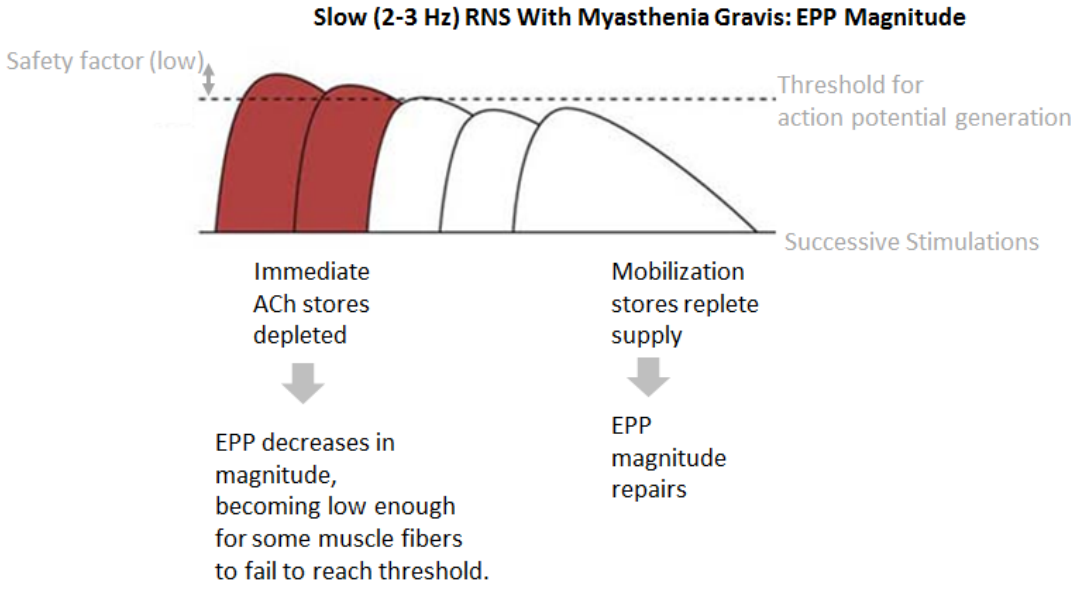
(Diagram modified from Preston and Shapiro 2012)

Repetitive Nerve Stimulation in a Post-Synaptic Disorder (e.g., myasthenia gravis)

In myasthenia gravis, poor acetylcholine receptor sensitivity leads to low EPPs.



In this compromised situation, slow RNS can decrease the EPP below the safety factor.

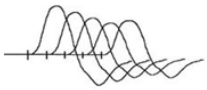


(Diagram modified from Preston and Shapiro 2012)

How does the diminishing EPP response affect the recorded CMAPs?

EPP magnitude → probability of MFAP firing → proportion of MFAPs firing → CMAP amplitude/area

Thus, the EPP decrement translates to a similar (U-shaped) CMAP decrement:



Result: U-shaped CMAP decrement

(Diagram modified from Preston and Shapiro 2012)

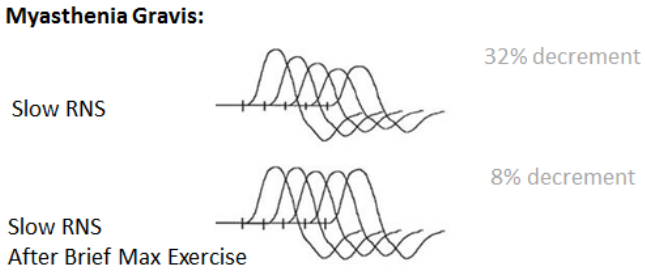
Post-exercise exhaustion increases the decrement, likely by further draining ACh mobilization stores.

Myasthenia Gravis: Prolonged maximal exercise (1 minute)

Baseline	1 min after max exercise	2 min after max exercise	3 min after max exercise
32% decrement	44% decrement	56% decrement	69% decrement

(Diagram modified from Preston and Shapiro 2012)

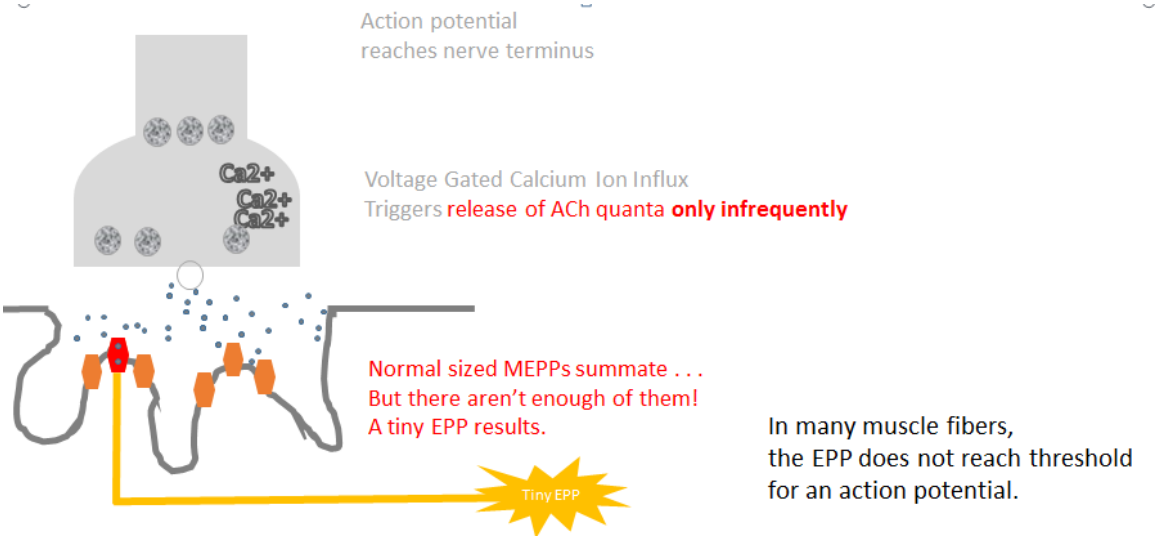
In contrast, brief maximal exercise repairs decrement through potentiation by increased calcium influx in the motor nerve terminus.



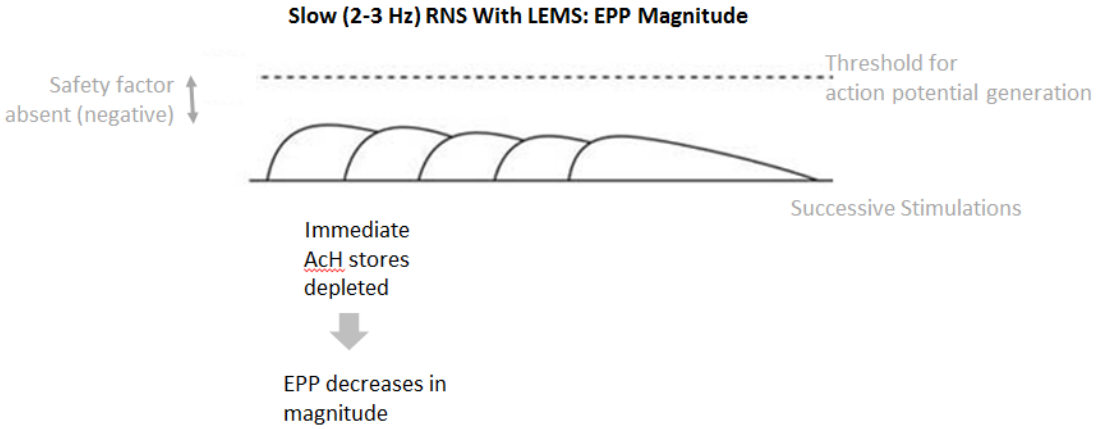
(Diagram modified from Preston and Shapiro 2012)

Repetitive Nerve Stimulation in a Pre-Synaptic Disorder (e.g., Lambert-Eaton myasthenic syndrome (LEMS))

In LEMS, calcium channel dysfunction leads to impaired ACh release.



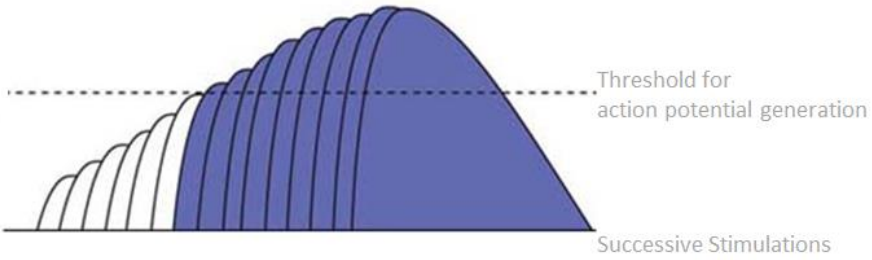
Slow RNS decreases EPP further below normal, which may further lower CMAP.



(Diagram modified from Preston and Shapiro 2012)

Brief maximal exercise or rapid RNS not only repairs the decrement, but results in a significant EPP increment above baseline. This is due to activation of NMJs that were failing to transmit at baseline.

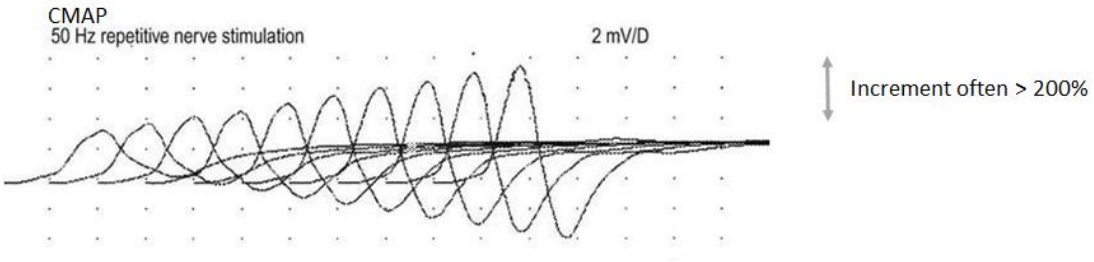
Rapid (50 Hz) RNS With LEMS: EPP Magnitude



Because at baseline, so many EPPs were below threshold, the potentiation is dramatic.

(Diagram modified from Preston and Shapiro 2012)

The dramatic potentiation is seen in recorded CMAPs:



Many muscle fibers previously not contributing to the CMAP (due to below-threshold EPPs) now participate.

(Diagram modified from Preston and Shapiro 2012)

In lieu of (painful) 50 Hz repetitive stimulation, brief (10 seconds) maximal exercise also achieves this increment:

CMAP Increment (ulnar motor NCS in LEMS):

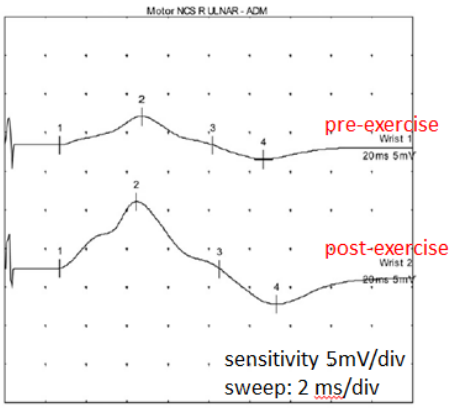


Image modified from Liang and Han (2013)

Needle EMG Findings

Single Fiber EMG (sfEMG)

Single fiber EMG is the most sensitive electrodiagnostic test for neuromuscular junction disorders. sfEMG records **individual muscle fiber action potentials** (MFAPs) during activation of a motor unit.

Conventional needle EMG	Records aggregate response of **many muscle fibers**
Single fiber EMG	Aims to isolate response of a **single muscle fiber**

↓

Muscle fiber action potential (MFAP)

In the setting of evaluation of neuromuscular junction disorders, we can use to assess **jitter** and **blocking**.

Jitter	variability of the interval between two muscle fiber potentials from the same motor unit increased in disorders of the neuromuscular junction and in early reinnervation

Blocking occurs when the second potential fails to appear. In the case of NMJ disorders, this can result from failure at the neuromuscular junction.

Example of jitter:

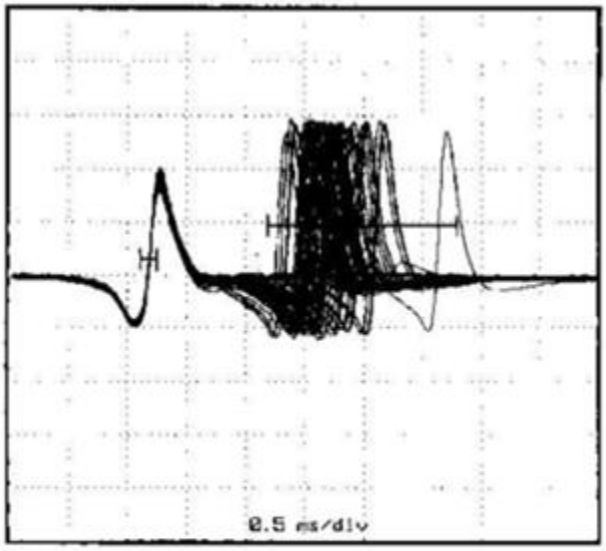


FIGURE 5. Single-fiber EMG recordings from the extensor digitorum communis muscle of a patient with myasthenia gravis; 55 oscilloscope traces are superimposed. Jitter is markedly increased, and there is occasional blocking.

Image from Sanders and Stålberg (1996)

Abnormal jitter:

Relative criteria:

- mean value of consecutive differences (MCD) of 20 fiber pairs ≥ 95% upper confidence limit
- jitter values exceed the 95% upper confidence limit in more than 10% of action potential pairs

Absolute criteria:

- blocking in more than one fiber
- jitter values exceeding 55 µs

Multiple physiologic factors affect jitter:

- age
- muscle selection
- temperature (jitter increases with cooling in normal subjects; however, in some disease states, it may increase with heating as well)
- ischemia (jitter increases with ischemia)
- in disease states, firing rate:
    - in post-synaptic disorders, it may increase (worsen) with increasing firing rate
    - in pre-synaptic disorders, it decreases (improves) with increasing firing rate

Findings on Standard Needle EMG

Standard needle EMG is often normal.

Abnormalities that can be observed include:

- **motor unit instability (jiggle):** this refers to variability in the morphology of a motor unit action potential each time it appears. It is the correlate of jitter and blocking, observed at the level of MUAPs (rather than single MFAPs). The variability in neuromuscular junction transmission across the NMJs that make up a motor unit gives rise to the changing morphology.
    - in particular, in pre-synaptic disorders, one can observe individual MUAPs that increase in amplitude as the firing rate increases
- **denervating potentials:** fibrillations and positive sharp waves can be seen in severe cases of myasthenia gravis and botulism, due to effective denervation due to NMJ failure
- **small amplitude, short duration MUAPs:** In addition, when blocking is severe enough to have multiple muscle fibers failing to contribute to a motor unit action potential, the MUAPs can resemble those observed in a myopathy: short-duration, low-amplitude units with early recruitment.

Works Cited

- Liang CL, Han S. Neuromuscular junction disorders. PM R. 2013 May;5(5 Suppl):S81-8.
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- Sanders DB, Stålberg EV. AAEM minimonograph #25: single-fiber electromyography. Muscle Nerve. 1996 Sep;19(9):1069-83.