Neuromuscular electrical stimulation (NMES) for healthy and cachectic muscles

Julien Gondin
Institut NeuroMyoGène (INMG)
UMR CNRS 5310 – INSERM 1217 - UCBL
Lyon, FRANCE
julien.gondin@univ-lyon1.fr
Evaluation of methods for electrical stimulation of human skeletal muscle in situ

E. Hultman¹, H. Sjöholm³, I. Jäderholm-Ik⁴, and J. Krynicki²

INPUT
Electrical pulse at the skin level

Activation of intramuscular nerve branches

OUTPUT
Muscle contraction
Motor axons
Sensory axons
Stimulation

Antidromic volley
Efferent pathway

High Frequency (>50 Hz)
High intensity

Healthy humans
Clinical applications
NMES on cancer cachexia

DISCOMFORT
Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal

C. Scott Bickel · Chris M. Gregory · Jesse C. Dean

**Motor unit recruitment**

- Synchronous
- Spatially-fixed / Quite superficial
- Non selective / Random

**Henneman's size principle**
Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal

C. Scott Bickel · Chris M. Gregory · Jesse C. Dean

Motor unit recruitment

- Synchronous
- Spatially-fixed / Quite superficial
- Non selective / Random

- Greater muscle fatigue (Theurel et al. 2007, Jubeau et al. 2008)
- Larger metabolic demand (Vanderthommen et al. 2003, Jubeau et al. 2015)
Mode of Stimulation

**SES**

**SDSS**

Reduction in muscle fatigue during transcutaneous neuromuscular electrical stimulation by spatially and sequentially distributing electrical stimulation sources

Dimitry G. Saymak - Robert Nguyen - Milos R. Popovic - Kel Masani
Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal

C. Scott Bickel · Chris M. Gregory · Jesse C. Dean

Motor unit recruitment

- Synchronous
- Spatially-fixed / Quite superficial
- Non selective / Random

Muscle damage
Comparison between voluntary and stimulated contractions of the quadriceps femoris for growth hormone response and muscle damage

Marc Jubeau,1 Alessandro Sartorio,2 Pier Giulio Marinone,2 Fiorenza Agosti,2 Jacques Van Hoecke,3 Kazunori Nosaka,4 and Nicola A. Maffiuletti4

In recent years, the acute stimulation (NMES) on neuromuscular and metabolic re-

Comparison between voluntary and stimulated contractions of the quadriceps femoris for growth hormone response and muscle damage

NMES: 40 isometric contractions
75Hz; 6.25 s on – 20 s off

Voluntary exercise at the same force output (26% MVC)
Evidence of skeletal muscle damage following electrically stimulated isometric muscle contractions in humans

Abigail L. Mackey,1 Jens Bojsen-Moller,1 Klaus Qvortrup,2 Henning Langberg,1 Charlotte Suetta,1 Kari K. Kalliokoski,3 Michael Kjaer,4 and S. Peter Magnusson1

STIMULATED ISOMETRIC CONTRACTIONS INDUCE MUSCLE DAMAGE

Gastrocnemius medialis muscle

30 minutes

60 Hz; 6 s on – 6 s off

Maximally tolerated stimulation intensity
Time Course of Central and Peripheral Alterations after Isometric Neuromuscular Electrical Stimulation-Induced Muscle Damage

Alexandre Foure1, Kazunori Nosaka2, Jennifer Wegrzyk1, Guillaume Duhamel1, Arnaud Le Troter3, Hélène Boudinet2, Jean-Pierre Mattei1,4, Christophe Vilmen1, Marc Jubeau5, David Bendahan1, Arnaud Le Troter3, Guillaume Duhamel1, David Bendahan1, Julien Gondin1

- 40 isometric contractions (5 s on/35 s off; 100 Hz)
- long muscle length
- Evoked-force: 32 ± 7% MVC
- Neuromuscular tests: MVC, Peak Doublet (Db100) & Voluntary Activation (VA)

*A significantly different from Baseline (P < 0.05)
Localization and quantification of intramuscular damage using statistical parametric mapping and skeletal muscle parcellation

Alexandre Fouré1, Arnaud Le Trotter1, Maxime Guye1,2, Jean-Pierre Mattei1,2, David Bendahan1 & Julien Gondin2

- 40 isometric contractions (5 s on/35 s off; 100 Hz)
- Long muscle length
- Evoked-force: 32 ± 7% MVC
- T2 MRI before (H0) and 4 days (H96) after NMES
Less indication of muscle damage in the second than initial electrical muscle stimulation bout consisting of isometric contractions of the knee extensors

Abdulaziz Aldayel · Marc Jubeau · Michael R. McGuigan · Kazunori Nosaka

40 isometric contractions
75Hz; 6.25 s on – 20 s off
2 sessions: D0 & D14
Myofibre damage in human skeletal muscle: effects of electrical stimulation versus voluntary contraction

R. M. Crameri1, 2, P. Aagaard3, K. Qvortrup4, H. Langberg5, J. Olesen6 and M. Kjær7

Experimental design (Quadriiceps)

- **VOL**: 210 maximal eccentric contractions
- **NMES**: 210 electrically-evoked (passive) lengthening contractions

Muscle biopsies

24h post- exercise
Whole-body NMES

Healthy humans

Clinical applications

NMES on cancer cachexia
Two Cases of Rhabdomyolysis After Training With Electromyostimulation by 2 Young Male Professional Soccer Players

Andreas Kästner, MD,* Markus Braun, MD,† and Tim Meyer, MD†

Case 1

✓ A professional German first league soccer player
✓ 20 min of WB-NMES
✓ Dark urine and reported severe muscle pain in the gluteal and femoral regions 2 days afterwards
✓ CK = 240 000 U/L (reference level, <370 U/L) reference level, >370 U/L
✓ The soccer player was taken to the intensive care unit and intravenous fluids (6-13 L electrolyte solution per day) were administered besides oral intake (6-15 L per day) for 4 days.

Case 2

✓ A 17-year-old member of the German U17 national soccer team
✓ 20 min of WB-NMES
✓ He suffered from modest muscle ache in the femoral region
✓ Elevated CK = 30 170 U/L
First NMES sessions should be performed at short muscle length

NMES should be performed under isometric conditions

NMES-induced lengthening contractions must be prohibited

Use different electrodes positionning
MINI REVIEW

Is high-frequency neuromuscular electrical stimulation a suitable tool for muscle performance improvement in both healthy humans and athletes?

Julien Gondin • Patrick J. Cozzone • David Bendahan

Control of training intensity (%MVC)
(Maffiuletti. 2010; Gondin et al. 2011)
NMES ≤ Voluntary resistance training

(Bax et al. 2005)
Electromyostimulation Training Effects on Neural Drive and Muscle Architecture

JULIEN GONDIN, MARIE GUETTE, YVES BALLAY, and ALAIN MARTIN
INSERM/ERM 207 Laboratory, Faculty of Sport Sciences, University of Burgundy, Dijon, FRANCE

Healthy humans

Clinical applications

NMES on cancer cachexia

12 young healthy men (23 yrs)
8-wk period - 4 sessions/wk
40 contractions - 6.25s on/20 s off – 75 Hz
Training intensity: 60-70% of the MVC

Tests: before (W0); after 4 (WK4) and 8 weeks (WK8) of NMES

* W4 > W0  $ W8 > W0  # W8 > W4
- Activation of several brain areas in a dose-response manner (Smith et al. 2003)
- Increased V-wave amplitudes (Gondin et al. 2006)
- Cross-education effect (Zhou et al. 2002)
Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis

Julien Gondin,1,2* Lorenzo Brocca,2* Elena Bellinzona,2 Giuseppe D’Antona,2 Nicola A. Maffioletti,4 Danilo Miotto,2 Maria A. Pellegrino,2 and Roberto Bottinelli2

8 healthy young men (26 yrs)
8-wk period - 3 sessions/wk
40 contractions - 6.25 s on/20 s off – 75 HZ
Training intensity: 55-60% MVC
Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis

Julien Gondin,1,2 Lorenzo Brocca,2 Elena Bellinzona,2 Giuseppe D’Antona,2 Nicola A. Maffioletti,4 Danilo Miotti,2 Maria A. Pellegrino,2 and Roberto Bottinelli2

**Healthy humans**

**Clinical applications**

**NMES on cancer cachexia**

- Strength gains
- Muscle hypertrophy
- Oxidative metabolism
- Antioxidant defense systems
- Mitochondrial biogenesis?
Key points

- Isometric strength gains
- Neural adaptations
- Muscle hypertrophy, remodelling...
- Functional changes (resistance to fatigue...)?
- Equally/Less effective than voluntary resistance training (Bax et al. 2005)

Relevant when the ability to perform voluntary contractions is difficult/impossible
Cachexia: A new definition

William J. Evans*, John E. Morley*, Josep Argilés*,
Connie Bales*, Vickie Baracos*, Denis Guttridge*,
Aminah Jatoi*, Kamyar Kalantar-Zadeh*, Herbert Lochs*,
Giovanni Mantovani*, Daniel Marks*, William E. Mitch*,
Maurizio Muscaritoli*, Armine Najand*, Piotr Ponikowski*,
Filippo Rossi Fanelli*, Morrie Schambelan*, Annemie Schols*,
Michael Schuster*, David Thomas*, Robert Wolfe*, Stefan D. Anker*

Definition

Cachexia is weight loss in adults without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (or BMI <20 kg/m²) for fluid retention and institute corrective measures to treat cachexia.

Anorexia

Inflammation

Insulin resistance

Hypogonadism

Anemia

FAT LOSS

MUSCLE WASTING

Weight loss

Weakness & Fatigue

reduced muscle strength, VO₂ max, and physical activity

CACHEXIA DIAGNOSIS

Weight loss of at least 5% in 12 months or less

- Decreased muscle strength
- Fatigue
- Anorexia
- Low fat-free mass index
- Abnormal biochemistry:
  - Increased inflammatory markers (CRP, IL-6)
  - Anemia (Hb <12 g/dL)
  - Low serum albumin (<3.2 g/dL)

3 of 5
Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease

Sarah Jones¹,², William D-C Man¹,², Wei Gao³, Irene J Higginson³, Andrew Wilcock⁴, Matthew Maddocks⁵

Figure 1. Forest plot of quadriceps muscle strength for NMES versus control.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NMES</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdellaoui 2011</td>
<td>8.4</td>
<td>3.5</td>
<td>1.24 [0.09, 2.40]</td>
</tr>
<tr>
<td>Bourjeily-Habr 2002</td>
<td>10.5</td>
<td>3.9</td>
<td>0.33 [-0.60, 1.26]</td>
</tr>
<tr>
<td>Greening 2014</td>
<td>1.17</td>
<td>0.69</td>
<td>0.06 [-0.14, 0.26]</td>
</tr>
<tr>
<td>Maddocks 2009a</td>
<td>7.4</td>
<td>-2</td>
<td>0.92 [-0.16, 2.00]</td>
</tr>
<tr>
<td>Maddocks 2013</td>
<td>0.6</td>
<td>-0.5</td>
<td>0.59 [-0.21, 1.40]</td>
</tr>
<tr>
<td>Maddocks 2016a</td>
<td>3.4</td>
<td>0.3</td>
<td>0.64 [0.08, 1.19]</td>
</tr>
<tr>
<td>Neder 2002</td>
<td>27.4</td>
<td>5.2</td>
<td>0.81 [-0.19, 1.81]</td>
</tr>
<tr>
<td>Nápolis 2011</td>
<td>0.2</td>
<td>1.6</td>
<td>-0.12 [-0.63, 0.39]</td>
</tr>
<tr>
<td>Quittan 2001</td>
<td>21.4</td>
<td>-8.9</td>
<td>2.18 [1.30, 3.07]</td>
</tr>
<tr>
<td>Sillén 2014a</td>
<td>10.8</td>
<td>6.1</td>
<td>0.33 [-0.18, 0.83]</td>
</tr>
<tr>
<td>Sillén 2014a</td>
<td>1.4</td>
<td>6.1</td>
<td>-0.45 [-0.97, 0.07]</td>
</tr>
<tr>
<td>Vivodtzev 2006</td>
<td>97</td>
<td>36</td>
<td>1.01 [-0.01, 2.04]</td>
</tr>
<tr>
<td>Vivodtzev 2012</td>
<td>11</td>
<td>-2.8</td>
<td>0.88 [-0.06, 1.83]</td>
</tr>
</tbody>
</table>

Total (95% CI) 398 383 100.0% 0.53 [0.19, 0.87]

Heterogeneity: Tau² = 0.23; Chi² = 42.80, df = 12 (P < 0.0001); I² = 72%
Test for overall effect: Z = 3.09 (P = 0.002)
**Functional and Muscular Effects of Neuromuscular Electrical Stimulation in Patients With Severe COPD**

A Randomized Clinical Trial

Isabelle Vivodtzev, PhD; Richard Deligeer, PhD; Philippe Gagnon, MSc; Vincent Manguy, MSc; Didier Saey, PhD; Annie Dubé, PhD; Marie-Ève Paré, MSc; Isabelle Vivodtzev, PhD; Richard Debigaré, PhD; Philippe Gagnon, MSc; Marthe Belanger, BSc; and François Maltête, MD

---

**Protocol**

- Severe COPD patients (n=20)
- 50 Hz, 5 days/wk for 6 weeks (vs. 5 Hz for Sham)
- NMES @ HOME (5% to 22% MVC)
- QF and calf muscles

---

**Main outcomes**

Muscle CSA, QF force & endurance, muscle tissue characteristics

---

**Main results**

Improvements in muscle mass, performance & exercise capacity

More favorable muscle anabolic to catabolic balance
Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial

Matthew Maddocks, Claire M Nolan, William D-C Man, Michael F Polkey, Nicholas Hart, Wei Gao, Gerard F Rafferty, John Moxham, Inme J Higginson

Protocol

- COPD patients (n= 25 NMES vs. n=27 Placebo; age: 70 years)
- QF NMES @ HOME: 50 Hz, 30 min, daily for 6 weeks. Intensity 0 to 120 mA (0-20 mA Placebo)
- NMES: 34 sessions, 923 min, 15-25%MVC

Main outcomes

6MWD, QF MVC, rectus femoris CSA, physical activity level

Main results

NMES improves functional exercise and enhances quadriceps muscle mass and function. Functional benefits during daily life
**Critical Illness Myopathy and GLUT4: Significance of Insulin and Muscle Contraction**

**Protocol**
- 50 Hz, 6 s on / 10 s off, 2 × 20 min/ day × 12 consecutive days
- Visible contractions: QF + tibialis (ICU < 2 days – SOFA > 8)

**Main outcomes**
- Muscle fiber CSA / GLUT-4 localization / AMPK

**Main result**
- Increased in type 2 CSA / GLUT4 detected at the sarcolemma & T-tubules (elevated p-AMPK)

---

No control of the training intensity (« visible contractions »)
Effects on muscle force, quality of life...?
Conclusions  NMES use in adult cancer survivors is an emerging field and current literature is limited by studies of poor quality and a lack of adequately powered RCTs. Existing evidence suggests that NMES is safe and may be more effective than usual care for improving HR-QoL. Prescription and progression should be tailored for the individual based on functional deficits.

Conflicting findings (methodological issues...)

No control of the electrically-evoked force level (Training Intensity)
Collaborators

- R. Bottinelli (Pavia)
- A. Fouré (Marseille)
- S. Grosprêtre (Besançon)
- M. Jubeau (Nantes)
- N. Maffiuletti (Zurich)
- A. Martin (Dijon)
- N. Place (Lausanne)

Thank you for your attention