

FES in Europe and beyond: Current Translational Research

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Abstract

Capacity of adult neural and muscle tissues to respond to external Electrical Stimulation (ES) is the biological basis for the development and implementation of mobility impairment physiotherapy protocols and of related assistive technologies, e.g. Functional Electrical Stimulation (FES). All body tissues, however, respond to electrical stimulation and, indeed, the most successful application of FES is electrical stimulation of the heart to revert or limit effects of arrhythmias (Pace-makers and Defibrillators). Here, we list and discuss results of FES current research activities, in particular those presented at 2016 Meetings: the PaduaMuscleDays, the Italian Institute of Myology Meeting, the 20th International Functional Electrical Stimulation Society (IFESS) conference held in Montpellier and the Vienna Workshop on FES. Several papers were recently e-published in the European Journal of Translational Myology as reports of meeting presentations. All the events and publications clearly show that FES research in Europe and beyond is alive and promises translation of results into clinical management of a very large population of persons with deficiencies.

Key Words: FES, denervated muscle, mobility impairment, aging, prevention and assistive technology, rehabilitation, biomedical technology

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Ability of neural and muscle tissues to respond to external Electrical Stimulation (ES) is the sound biological basis of established therapeutic managements of mobility impairments, assistive technology and of the current research activities aimed to extend its clinical applications. All the body tissues, however, respond to ES and, indeed, the most successful application of Functional Electrical Stimulation (FES), though known under other names or acronyms, is the electrical stimulation of the heart to revert or limit effects of arrhythmias (Pace-makers and Defibrillators). We would like to list and discuss here results of current research activities on FES, in particular those published in the European Journal of Translational Myology after presentation during the 2015 XI Meeting of the Italian Institute of Myology (IIM),¹ the 2016 Spring PaduaMuscleDays,² the 2016 Vienna FES Workshop and the 2016 International Conference of IFESS society held in Montpellier France.³

In Table 1 are listed the subtopics of FES research and applications published in the European Journal of

Translational Myology that will be discussed in the following sections. They are only some of a much longer list that represent the many subtopics of FES, i.e., i) Biological bases of FES for Neuromuscular Mobility Impairments; ii) FES for Arm, Leg and Body Motility; iii) FES for Swallowing, Micturition, Gastric function restoration; iv) FES as a countermeasure of muscle weakness and atrophy; v) FES and mechanical devices (wearable robots, cycles...); vi). FES for Pain Management; vii) Sensor interfaces to control FES (BCI, EMG, IMU and more); viii) FES advanced technology to improve efficiency and selectivity.

2015 XI Meeting of IIM, Italy and 2016 Spring PaduaMuscleDays

Among other scientific topics, during the 2015 IIM meeting the molecular mechanisms of muscle atrophy, wasting and diseases were deeply discussed. One of the remarkable features of skeletal muscle is, indeed, the capacity to adapt its morphological, biochemical, and molecular properties in response to several events.

Table 1. List of subtopics of Functional Electrical Stimulation research and management

1. Biological bases of FES for neuromuscular mobility impairments
2. FES for upper and lower body mobility
3. FES for swallowing, micturition, gastric and other vital functions
4. FES as a countermeasure of muscle atrophy, weakness and aging
5. FES combined with mechanical devices (wearable robots, cycles and more ...)

However, under pathological conditions skeletal muscle loses its adaptability, leading to atrophy and wasting. The continual synthesis and degradation of cell proteins is the result of normal intracellular metabolism and represents an important homeostatic function of muscle tissue. Muscle wasting, in contrast, is a process in which the delicate balance between anabolic and catabolic processes is impaired. In recent years, age-related diseases and disabilities have become of major interest and importance for health. The pathological process associated with aging is known as sarcopenia, characterized by a progressive loss of mobility and a decrease of the life quality. Society at large will benefit from delaying, as much as possible, the sarcopenia economic and social consequences. In elderly, muscles become atrophic (loss in muscle mass) and weaker (loss in muscle force), more susceptible to damage and consequently regenerate and recover more slowly than in younger individuals.⁴

During the IIM-Myology meeting, several signaling pathways have been discussed as key maintenance regulators of muscle mass or triggers of muscle wasting.¹ Nevertheless, despite the new discoveries in this field, no effective therapies are still available. Therefore, it is of fundamental importance to gain greater knowledge about the cellular and molecular processes controlling this debilitating condition to find effective countermeasures.⁵ FES is one of the approaches that attracted much attention in the last 10 years, based on practical considerations: i) ES can be applied to people that cannot carry out normal physical activity; ii) it modulates similar factors associated with physical exercise; iii) it improves muscle mass and function in sedentary elderly people. In particular, it has been demonstrated that ES activates, at the level of skeletal muscle, the growth factor IGF-1, which in turn promotes anabolic pathways increasing protein synthesis while reducing protein degradation. IGF-1 and FES appear to be responsible for the increase in muscle performance. Interestingly, ES, similarly to physical exercise, attenuates the functional decline associated

with aging, improving muscle strength and mass, maintaining the overall size of muscle fibers (decreasing during aging), activating satellite cells and guaranteeing muscle adaption.⁶ Based on several evidences, we can also speculate that FES mimics the effects of endurance training, since they do not induce muscle damage, and activate comparable molecular networks.

Many of these mechanisms were discussed in recent papers published in the European Journal of Translational Myology and during the 2016Spring PaduaMuscleDays as the main determinants of the positive effects of physical exercise and FES when applied to therapeutic and rehabilitation strategies aimed to prevent or revert the consequences of aging and mobility impairments.^{2,3,7-15}

20th Conference of the International Functional Electrical Stimulation Society, IFESS - 2016

The International Functional Electrical Stimulation Society (IFESS) is an inter-professional and collaborative organization, whose main objective is promotion of research, applications and understanding of electrical stimulation as it is utilized in the field of medicine.³

The theme of the 20th IFESS conference, organized in Montpellier, France in 2016 by INRIA institute and Montpellier university was «Hybrid Approaches of IFESS». The idea being to highlight ongoing research activities associating FES to other assistive approaches such as exoskeletons or central nervous system (CNS) stimulation. The notion of hybridity can also be seen from the perspective of the multidisciplinary face of the field. Three special sessions were dedicated specifically to this theme with articles associating FES to 1) wearable robotics, 2) CNS stimulation and 3) cycling devices. Electrical stimulation can be applied in a large panel of situations and some of the emerging applications have been presented in the special session: “Emerging FES interventions, with original and promising studies”. Electrical stimulation activates both efferent and afferent pathways. This property is extremely appealing in the context of functional rehabilitation and neurological recovery. The engagement of patients is mandatory to increase the potential of the training. This was the object of the special session “FES and fun” which explores different approaches to motivate the patients to actively participate into their rehabilitation protocol. In the regular sessions, articles insisted in the recent advances in technology to improve stimulation efficiency and selectivity, to explore new modalities and applications of FES. Engineers and Clinicians demonstrated in their articles the importance and potential of this very active research field. We wish to thank all authors of the articles that have contributed to EJTM (Tables 2 to 7) and for making the Ejtm Special Section on 2016 IFESS Conference an exciting and intriguing read.^{9,16-64}

Table 2. *European Journal of Translational Myology, 2016. FES papers: Subtopic 1. Biological bases of FES for neuromuscular mobility impairments*

Review	Carraro U, Kern H. Severely atrophic human muscle fibers with nuclear misplacement survive many years of permanent denervation. <i>Eur J Transl Myol</i> 2016;26:76-80. ¹⁵
Article	Zampieri S, Mosole S, Löfler S, et al. Physical Exercise in Aging: Nine Weeks of Leg Press or Electrical Stimulation Training in 70 Years Old Sedentary Elderly People. <i>Eur J Transl Myol</i> 2015; 25: 237–242. doi: 10.4081/ejtm.2015.5374. ⁹
Review	Barberi L, Scicchitano BM, Musaro A. Molecular and Cellular Mechanisms of Muscle Aging and Sarcopenia and Effects of Electrical Stimulation in Seniors. <i>Eur J Transl Myol</i> 2015;25:231-6. doi: 10.4081/ejtm.2015.5227. ¹⁶
Article	Tramonti C, Rossi B, Chisari C. Extensive functional evaluations to monitor aerobic training in Becker Muscular Dystrophy: A case report. <i>Eur J Transl Myol</i> 2016;26:81-6. ¹⁷
Article	Hiroux C, Vandoorne T, Koppo K, De Smet S, Hespel P, Berardi E. Physical activity counteracts tumor cell growth in colon carcinoma C26-injected muscles: an interim report. <i>Eur J Transl Myol</i> 2016;26:67-75. ¹⁸
Review	Coletti D, Daou N, Hassani M, Li Z, Parlakian A, Serum Response Factor in muscle tissues: from development to ageing. <i>Eur J Transl Myol</i> 2016;26:87-92. ¹⁹
Article	Guiho T, Azevedo Coste C, Delleci C, Chenu J-P, Vignes J-R, Bauchet L, Guiraud D. An intermediate animal model of spinal cord stimulation. <i>Eur J Transl Myol</i> 2016;26:150-4. ²⁰
Article	Totzeck A, Mummel P, Kastrup O, Hagenacker T. Clinical features of neuromuscular disorders in patients with N-type voltage-gated calcium channel antibodies. <i>Eur J Transl Myol</i> 2016;26:301-6. ²¹
Article	Carotenuto F, Coletti D, Di Nardo P, Teodori L. α -linolenic acid reduces TNF-induced apoptosis in C2C12 myoblasts by regulating apoptotic proteins expression. <i>Eur J Transl Myol</i> 2016;26:317-22. ²²
Article	Lavorato M, Gupta PK, Hopkins PM, Franzini-Armstrong C. Skeletal muscle microalterations in patients carrying Malignant Hyperthermia-related mutations of the e-c coupling machinery. <i>Eur J Transl Myol</i> 2016;26:323-32. ²³
Review	Scicchitano BM, Sica G, Musarò A. Stem cells and tissue niche: two faces of the same coin of muscle regeneration. <i>Eur J Transl Myol</i> 2016;26:333-8. ¹⁵

12th Vienna International Workshop on FES, September 8th-9th, 2016

The "Vienna Workshop on Functional Electrical Stimulation" was held the first time in 1983 in Vienna, Austria. Since then it is organized by the Center for Medical Physics and Biomedical Engineering (former: Center for Biomedical Engineering and Physics), the Medical University of Vienna and the Austrian Society for Biomedical Engineering every three years in Vienna or locations close to Vienna. This scientific conference provides a platform for researchers to present and discuss their recent work whilst visitors can expect a representative and actual overview of the state of the art of FES. Traditionally, parallel sessions are avoided. Since the 10th Workshop (2010) all conference proceedings are available on DVD: "30 years of FES history on one click" (<http://fesworkshop.org>).

This year's Workshop was held at the renovated Campus of the Medical University Vienna, a place with a long history in medical research.

The conference started with two Pre - Conference Courses "FES of Denervated Muscles – An Essential Therapeutic Option after Peripheral Nerve Lesion", (Organizers: Mayr W., Krenn M., Biowski P., all from Vienna, Austria) and "Non invasive posterior root stimulation for assessment and modulation of spasticity and motor control" (Organizers: Mayr W., Krenn M., both Vienna, Austria and Dimitrijevic M., Houston, TX, USA) designed as hands - on workshops with a comprehensive introduction on physiological, clinical and technical basics, safety issues, handling of equipment, guidelines and protocols.

As FES of denervated muscles differs fundamentally from classical neuromuscular ES, the main particularities were addressed in an open interactive discussion, scientifically based on the strong clinical, functional and structural results of the EU Program RISE^{6-8 6-8}.

Table 3. *European Journal of Translational Myology, 2016. FES papers of Subtopic 2. Body and leg motility*

Article	Laubacher M, Aksöz EA, Binder-Macleod S, Hunt KJ. Comparison of proximally versus distally placed spatially distributed sequential stimulation electrodes in a dynamic knee extension task. Eur J Transl Myol 2016;26:110-115. ²⁶
Article	Schweigmann M, Kirchhoff F, Koch KP. Modeling and Simulations in Time Domain of a Stimulation Set-up for Cortical Applications. Eur J Transl Myol 2016;26:116-21. ²⁷
Article	Sijobert B, Azevedo-Coste C, Andreu D, Verna C, Geny C. Effects of sensitive electrical stimulation based cueing in Parkinson's disease: a preliminary study. Eur J Transl Myol 2016;26:122-8. ²⁸
Article	Kumar D, Verma S, Bhattacharya S, Lahiri U. Audio-visual stimulation in conjunction with functional electrical stimulation to address upper limb and lower limb movement disorder. Eur J Transl Myol 2016;26:140-4. ²⁹
Article	Kumar D, Dutta A, Das A, Lahiri U. Engagement sensitive visual stimulation. Eur J Transl Myol 2016;26:145-9. ³⁰
Article	Bhattacharyya S, Clerc M, Hayashibe M. A study on the effect of electrical stimulation as a user stimuli for motor imagery classification in Brain-Machine Interface. Eur J Transl Myol 2016;26:165-8. ³¹
Article	Muthalib M, Kerr G, Nosaka K, Perrey S. Local muscle metabolic demand induced by neuromuscular electrical stimulation and voluntary contractions at different force levels: a NIRS study. Eur J Transl Myol 2016;26:169-74. ³²
Article	Malešević J, Štrbac M, Isaković M, Kojić V, Konstantinović L, Vidaković A, Dedijer S, Kostić M, Keller T. Evolution of surface motor activation zones in hemiplegic patients during 20 sessions of FES therapy with multi-pad electrodes. Eur J Transl Myol 2016;26:175-80. ³³
Article	Peri E, Ambrosini E, Pedrocchi A, Ferrigno G, Nava C, Longoni V, Monticone M, Ferrante S. Can FES-augmented active cycling training improve locomotion in post-acute elderly stroke patients? Eur J Transl Myol 2016;26:187-92. ³⁴
Article	Li Z, Guiraud D, Andreu D, Fattal C, Gelis A, Hayashibe M. A hybrid functional electrical stimulation for real-time estimation of joint torque and closed-loop control of muscle activation. Eur J Transl Myol 2016;26:193-6. ³⁵
Article	Araujo Guimarães J, Oliveira da Fonseca La, Cardoso dos Santos-Couto-Paz C, Padilha Lanari Bó A, Fattal C, Azevedo-Coste C, Fachin-Martins E. Towards parameters and protocols to recommend FES-Cycling in cases of paraplegia: a preliminary report. Eur J Transl Myol 2016;26:209-14. ³⁶
Article	Dali M, Rossel O, Guiraud D. Fast simulation and optimization tool to explore selective neural stimulation. Eur J Transl Myol 2016;26:215-8. ³⁷
Article	Cho W, Sabathiel N, Ortner R, Lechner A, Irimia DC, Allison BZ, Edlinger G, Guger Ch. Paired Associative Stimulation using Brain-Computer Interfaces for Stroke Rehabilitation: A Pilot study. Eur J Transl Myol 2016;26:219-22. ³⁸
Article	Aksöz EA, Laubacher M, Binder-Macleod S, Kenneth J. Hunt Effect of stochastic modulation of inter-pulse interval during stimulated isokinetic leg extension. Eur J Transl Myol 2016;26:229-34. ³⁹
Article	Julémont N, Nonclercq A, Delchambre V, Vanhoostenberghe A. A study on cross-talk nerve stimulation: electrode placement and current leakage lid. Eur J Transl Myol 2016;26:239-43. ⁴⁰
Article	Dautrebande M, Doguet P, Gorza S-P, Delbeke J, Botquin Y, Nonclercq A. In vivo photonic stimulation of sciatic nerve with a 1470 nm Laser. Eur J Transl Myol 2016;26:244-8. ⁴¹
Article	Stratton K, Faghri PD. Electrically and hybrid-induced muscle activations: effects of muscle size and fiber type. Eur J Transl Myol 2016;26:249-54. ⁴²
Article	Laursen CB, Nielsen JF, Andersen OK, Spaich EG. Feasibility of using Lokomat combined with functional electrical stimulation for the rehabilitation of foot drop. Eur J Transl Myol 2016;26:268-73. ⁴³

The goal was to train qualified medical staff to a level that allows confident, safe and efficient clinical application of the introduced methods.

The scientific program started with two special topics on *Functional Rejuvenation in Aging* and *Electrical Stimulation in Neuromuscular Disorders*. Then it

continued with a special session where the outcomes of the EU project *RETRAINER* (<http://www.retrainer.eu/>) were introduced with enough time to get in touch with the project leaders and to try out first prototypes for robotic supported reaching and grasping training.

Table 4. *European Journal of Translational Myology, 2016. FES papers of Subtopic 3. Arm motility*

Article	Lopes ACG, Ochoa-Diaz C , Baptista RS, Fonseca LO, Fattal C, Azevedo Coste C, Bó APL, Fachin-Martins E. Electrical stimulation to reduce the overload in upper limbs during sitting pivot transfer in paraplegic: a preliminary study. Eur J Transl Myol 2016;26:278- 82. ⁴³
Article	Isaković M, Belić M, Štrbac M, Popović I, Došen S, Farina D, Keller T. Electrotactile feedback improves performance and facilitates learning in the routine grasping task. Eur J Transl Myol 2016;26:197-202. ⁴⁴
Article	Gui K, Yokoi H, DZhangD. Human-FES cooperative control for wrist movement: a preliminary study. Eur J Transl Myol 2016;26:235-8. ⁴⁵
Article	Marquez-Chin C, Marquis A, Popovic MR. BCI-Triggered functional electrical stimulation therapy for upper limb. Eur J Transl Myol 2016;26:274-7. ⁴⁶

Table 5. *European Journal of Translational Myology, 2016. FES papers: Subtopic 3. FES for swallowing, and other applications*

Article	Schultheiss C, Schauer T, Nahrstaedt H, Seidl RO, Bieler J. Efficacy of EMG/Bioimpedance-Triggered Functional Electrical Stimulation on Swallowing Performance. Eur J Transl Myol 2016;26:283-6. ⁴⁷
Article	Riebold B, Nahrstaedt H, Schultheiss C, Seidl RO, SchauerT. Multisensor Classification System for Triggering FES in Order to Support Voluntary Swallowing. Eur J Transl Myol 2016;26:287-91. ⁴⁸
Article	Lonys L, Vanhoestenbergh A, Huberty V, Hiernaux M, Cauche N, Julémont N, Debelle A, Huberland F, Acuña V, Godfraind C, Devière J, Delchambre A, Mathys P, Nonclercq A. Design and implementation of a less invasive gastrostimulator. Eur J Transl Myol 2016;26:129-33. ⁴⁹
Article	Andrews B, Shippen J, Armengol M, Gibbons R, Holderbaum W, Harwin W. A Design Method for FES Bone Health Therapy in SCI. Eur J Transl Myol 2016;26:297-300. ⁵⁰

The following sessions covered findings in *Basic Research, Neuromodulation, Rehabilitation strategies, FES Exercise* and in the more hardware oriented part *Technologies, Engineering, Sensors*.

Three excellent keynote speakers provided insight into latest findings in FES and neighboring fields.

Jarvis J. (Liverpool, GB) introduced the potential of genomics, metabolomics and proteomics technologies to better understand cell biology in his talk "Neuromuscular cell biology and "omic technologies".

Lukanović A. (Ljubljana, Slovenia) discussed "Neuromodulation in the treatment of pelvic floor dysfunctions" and Podesser B. (Vienna, Austria) talked about "Animal research in FES" and the related

possibilities and regulations.

Details of the program of the 12th Vienna International Workshop on FES, September 8th-9th, 2016 are available at the link: <http://2016.fesworkshop.org/>

Conclusions

Altogether, evidence demonstrates that FES basic, translational and clinical research in Europe and beyond is alive. Translation of results to clinical therapies for a large population of patients is much more than a hope.

Author's contributions

All authors equally organized the draft and wrote the typescript.

Table 6. *European Journal of Translational Myology, 2016. FES papers of Subtopic 4. FES as a countermeasure of muscle weakness, atrophy and aging*

Myo News	XII IIM - Myology Meeting, October 1st to 4th 2015 - Reggio Emilia (Italy), Abstracts. Eur J Transl Myol 2016;26:2-24. ¹
Myo News	2016Spring PaduaMuscleDays, April 13th to 16th - Terme Euganee, Padova (Italy), Abstracts. Eur J Transl Myol 2016;26:37-60. ²
Article	Edmunds KJ, Gíslason MK, Arnadottir ID, Marcante A, Piccione F, Gargiulo P. Quantitative Computed Tomography and image analysis for advanced muscle assessment. Eur J Transl Myol 2016;26:93-100. ⁵¹

Table 7. *European Journal of Translational Myology, 2016. FES papers of Subtopic 6. FES Technology*

Article	Salchow C, Valtin M, Seel T, Schauer T. A new semi-automatic approach to find suitable virtual electrodes in arrays using an interpolation strategy. <i>Eur J Transl Myol</i> 2016;26:134-9. ⁵²
Article	Godfraind C, Debelle A, Lonys L, Acuña V, Doguet P, Nonclercq A. Inductive powering of subcutaneous stimulators: key parameters and their impact on the design methodology. <i>Eur J Transl Myol</i> 2016;26:155-60. ⁵³
Article	Oliveira A, Ordonez JS, Ashouri Vajari D, Eickenscheidt M, Stieglitz T. Laser-induced carbon pyrolysis of electrodes for neural interface systems. <i>Eur J Transl Myol</i> 2016;26:181-6. ⁵⁴
Article	Godfraind C, Debelle A, Lonys L, Acuña V, Doguet P, Nonclercq A. Inductive powering of subcutaneous stimulators: key parameters and their impact on the design methodology. <i>Eur J Transl Myol</i> 2016;26:155-60. ⁵⁵
Article	Valtin M, Kociemba K, Behling C, Kuberski B, Becker S, Schauer T. RehaMovePro: A versatile mobile stimulation system for transcutaneous FES applications. <i>Eur J Transl Myol</i> 2016;26:203-8. ⁵⁶
Article	Oliveira A, Ordonez JS, Ashouri Vajari D, Eickenscheidt M, Stieglitz T. Laser-induced carbon pyrolysis of electrodes for neural interface systems. <i>Eur J Transl Myol</i> 2016;26:181-6. ⁵⁷
Article	Aqueveque P, Acuña V, Saavedra V, Debelle A, Lonys L, Julémont N, Huberland F, Godfraind C, Nonclercq A. Power strategy in DC/DC converters to increase efficiency of electrical stimulators. <i>Eur J Transl Myol</i> 2016;26:223-8. ⁵⁸
Article	Julémont N, Nonclercq A, Delchambre V, Vanhoostenberghe A. A study on cross-talk nerve stimulation: electrode placement and current leakage lid. <i>Eur J Transl Myol</i> 2016;26:239-43. ⁵⁹
Article	Resquín F, Gonzalez-Vargas J, Ibáñez J, Brunetti F, Pons JL. Feedback error learning controller for functional electrical stimulation assistance in a hybrid robotic system for reaching rehabilitation. <i>Eur J Transl Myol</i> 2016;26:255-61. ⁶⁰
Article	Aqueveque P, Sobarzo S, Saavedra F, Maldonado C, Gómez B. Android platform for realtime gait tracking using inertial measurement units. <i>Eur J Transl Myol</i> 2016;26:262-7. ⁶¹
Article	Laursen CB, Nielsen JF, Andersen OK, Spaich EG. Feasibility of using Lokomat combined with functional electrical stimulation for the rehabilitation of foot drop. <i>Eur J Transl Myol</i> 2016;26:268-73. ⁶²
Article	Marquez-Chin C, Marquis A, Popovic MR. BCI-Triggered functional electrical stimulation therapy for upper limb. <i>Eur J Transl Myol</i> 2016;26:274-7. ⁶³
Article	Debelle A, Hermans L, Bosquet M, Dehaeck S, Lonys L, Scheid B, Nonclercq A, Vanhoostenberghe A. Soft Encapsulation of Flexible Electrical Stimulation Implant: Challenges and Innovations. <i>Eur J Transl Myol</i> 2016;26:292-6. ⁶⁴

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Conflict of Interest

The authors declare no potential conflict of interests.

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