Eur J Transl Myol 2020; 30 (4): 9437. doi: 10.4081/ejtm.2020.9437

30 Years of Translational Mobility Medicine: 2020 Padua Muscle Days go virtual from Euganean Hills, November 19th to 21st

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Abstract

In the autumn of 2019, the 2020 Padua Muscle Days (PMDs) were planned to be held from March 18 to March 21, 2020. The program listed Scientific Sessions to occur over three full days at either Padova University or the Hotel Augustus on Euganei Hills (Padova), Italy. Abruptly, however, in early January the Coronavirus COVID-19 outbreak started in China and changed the world perspectives. In Italy, the epidemia had the first Italian cases and victims in an area south of Milan and in a Village of the Euganei Hills (Vo Euganeo, Padova). Thus, it was a mandatory decision to post-pone the PMDs meeting to 19-21 November, 2020. Luckily, almost all chairs, speakers, and attendees accepted the decision and have assured their presence in late November by long-distance communications. Thus, the Collection of Abstracts were e-published in 30 (1) 2020 Issue of the European Journal of Translational Myology (EJTM) together with the many EJTM Communications submitted by speakers and attendees of the 2020 PMDs Here we add a few new entries and the detailed Program of the 2020 Virtual PMDs to be organized November 19-21, 2020 from the Hotel Petrarca of Euganei Hills (Padova), Italy. The Program of the 2020 Virtual PMDs ends with invitation by Zipora Yablonka-Reuveni and myself to the 2021 (Virtual) Padua Muscle Days, March 25-27, Euganei Hills (Padova), Italy.

Key Words: Translational Myology and Mobility Medicine, COVID-19 in 2020, Padua Muscle Days, Program & New Abstracts

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A series of meetings concerning muscle biology, physiology, medicine and rehabilitation, called Padua Muscle Days (PMDs), were initiated more than 30 years ago, specifically to provide experts' advices on Translational Myology and Mobility Medicine. Always the interest was on implementing basic research and trials to help prevent mobility disorders and/or to manage or rehabilitate young adults and elderly persons suffering from mobility disorders. Thus, the organizers of the 2020 PMDs implemented an intense program to be held from March 18 to March 21, 2020 either in Padova University or in the Hotel Augustus on Euganei Hills (Padova), Italy.[1] Abruptly, however, the Coronavirus COVID-19 outbreak, quickly spread and changed the world perspectives. In Italy the virus was first detected in Lombardy and VenetoW within a week, the COVID-2019 affected the first Italian victims in an area south of Milan and in a village of the Euganei Hills (Vo Euganeo, Padova). The village was immediately quarantined, but it was too late. The virus was spreading through the area. Thus, the PMDs was post-poned to 19-21 November, 2020, and the only option was to reprogram the list of presentations of the 2020 PMDs by long-distance communication to maintain international relations when the epidemia worsened again in Autumn. Luckily, chairs, speakers and attendees accepted the decision and have assured their virtual presence. The changes in the PMDs November 19-21 Program are the new dates and a reorganized schedule of the eight Sessions to allow, a world-wide attendance, to follow the Sessions during their mornings or afternoons. The Collection of Abstracts was e-published in the 30 (1) 2020 Issue of the European Journal of Translational Myology together with the many EJTM Communications submitted by Speakers and Attendees of the 2020PMDs.[1] Here we list, beside a few new Abstracts, the updated Program of the 2020 Virtual PMDs to be held November 19-21, 2020 from the Hotel Petrarca of Euganei Hills (Padova), Italy. The last Virtual Presentation will be invitation by Zipora Yablonka-Reuveni and myself to the 2021 (Virtual) Padua Muscle & Mobility Medicine Days (2021 V-PM3Ds), March 25-27, Euganei Hills (Padova), Italy.

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European Journal of Translational Myology - eISSN 2037-7460 - ISSN 2037–7452 – BAM On-Line

University of Padova, Italy Interdepartmental Research Center of Myology (CIR Myo)

Physiko&Rheumatherapie, Inst. f. Phys. Med., St. Pölten & Ambulante Reha, Amstetten, Austria

Easy Aging

A&C M-C Foundation for Translational Myology

2020 PaduaMuscleDays, November 25-28, Euganei Hills and Padova, Italy

MOBILITY MEDICINE: 30 YEARS OF TRANSLATIONAL RESEARCH

Euganei Hills, Padova (Italy), November 19 - 21, 2020

Hotel Petrarca, Piazza Roma 23, Montegrotto Terme, Euganei Hills (Padova) 35122 Italy
Phone +39 049 891 1744 - Email: petrarca@hotelpetrarca.it - https://www.hotelpetrarca.it/
Organizers: Ugo Carraro, Helmut Kern, Christiaan Leeuwenburgh, Marco Narici, Feliciano Protasi, Marco Sandri, Lee Sweeney


THURSDAY November 19, 2020

2020 Padua Muscle Days go Virtual: Italy Morning = Japan Afternoon

Italy 09.20 AM; Iceland 08.20AM; USA ET 02.20 AM; Japan 04.20 PM

Italy 09:20 AM **2020 Padua Muscle Days during the COVID-2020 Outbrek**, *Ugo Carraro*

Japan 04:30 PM Challenge of Osato Research Institute for Preventive Medicine with the aim to reduce medical costs in super-aging societies, *Yuki Hayashi, Gifu, Japan*

Japan 05:00 PM Dietary Phosphorus Overload Aggravates the Phenotype of the Dystrophin-Deficient mdx Mouse. Therapeutic effect of calcium and Vitamin C on muscle degeneration in elevated Pi or at low temperature cultures, *Ryoichi Matsuda, Department of Life Sciences, University of Tokyo, Japan*

Italy 10:30 AM The DLK1-DIO3 cluster miRNAs regulate mitochondrial functions in the dystrophic muscle in DMD*, Ai Vu Hong, Nathalie Bourg, Peggy Sanatine, Jerome Poupiot, Karine Charton, Evelyne Gicquel, Marco Spinazzi, Isabelle Richard, David Israeli, Evry, France*

Italy 11:00 AM Single-cell analysis revealed the importance of non-coding RNAs for muscle plasticity, *Stefano Cagnin, Biology, University of Padova, Italy*

Italy 11:30 AM Relationship between ETFDH mutations, expression levels of serum myomiRNAs and response to treatment in MADD patients, *Sara Missaglia, et al., Milan, Padova, Venice, Italy*

Italy 12:00 AM Blood contamination of human mouth fluid: a non-invasive approach for serological analyses in old and very old persons*, Barbara Ravara, et al., A&C M-C Foundation, Padova, Italy*

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THURSDAY November 19, 2020

2020 Padua Muscle Days go Virtual: Italy Afternoon = USA Morning

Italy 03.00 PM; Iceland 02.00 PM; USA ET 08.00 AM; Japan 10.00 PM

USA ET 08:00 AM — *SARCOPENIA AND AGING: Nutritional, Pharmacological and Physiological Interventions*

Christiaan Leeuwenburgh, Russ Hepple, Chairs

USA ET 8:00 AM — Effects of epicatechins on endothelial, mitochondrial and physical function: Clinical Trial Results. *Christiaan Leeuwenburgh, University of Florida, Gainesville, FL, USA*

USA ET 8:30 AM — The impact of Fermented Papaya Product (FPP) on cognitive and brain function in older adults: a pilot clinical trial, *Adam J. Woods, University of Florida, Gainesville, FL, USA*

USA ET 9:00 AM — Mitochondrial Permeability Transition causes muscle atrophy in advanced age, *Russel T. Hepple, University of Florida, Gainesville, USA*

USA ET 9:30 AM — Neuromuscular activity of C. elegans and zebrafish models of *FBXL4*-based mitochondrial respiratory chain disease: translational platforms for drug screening, *Manuela Lavorato et al., Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA*

Italy 5:00 PM — Impact of ageing and exercise on the neuromuscular junction, *Marco Narici, Department of Biomedical Sciences, Padua University, Italy*

Italy 5:30 PM — Neurohypophyseal hormones and skeletal muscle: a tale of two faces, *Sergio Adamo, Sapienza University of Rome, Italy*

Italy 6:00 PM — A role for fermented papaya in preventing and treating aging and cancer cachexia, through a potent and systemic antioxidant effect, *Mariantonia Logozzi et al., Istituto Superiore di Sanità, Rome, Italy*

USA ET 11:30 AM — Prospects for exercise training in the absence of muscle IGF-1, *Elisabeth R. Barton, Dept. of Applied Physiology & Kinesiology, University of Florida, Gainesville, USA*

Italy 7:00 PM — A possible strategy to prevent skeletal muscle atrophy induced by immobilization, *Paula Tavares, Faculty of Sport Sciences and Physical Education, University of Coimbra, Portugal*

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Hotel Petrarca, Euganei Hills, (Padova), Italy

FRIDAY November 20, 2020

Virtual-Presentations: Italy Morning = Japan Afternoon

Italy 09.00 AM; Iceland 08.00 AM; USA ET 03.00 AM; Japan 14.00 PM

Italy 9:30 AM ***Commitment to reproducibility in targeting mitochondrial respiratory control: basic and advanced applications of the O2k-FluoRespirometer***

Italy 9:20 AM Forewords, *Ugo Carraro, A&C M-C Foundation, Padova, Italy*

Italy 9:30 AM Commitment to reproducibility in mitochondrial respiration studies with permeabilized muscle fibers, *Carolina Doerrier, Marco Di Marcello, Erich Gnaiger, Oroboros Instruments, Innsbruck, Austria*

Italy 10:30 AM Mitochondrial ROS production, *Nina Kaludercic, CNR Neuroscience Institute, University of Padova, Italy*

Italy 11:00 AM Age-related changes of mechanical stiffness of extra-cellular matrix in human skeletal muscle, *Lorenzo Marcucci, et al., Department of Biomedical Sciences, Padua University, Italy*

Italy 11:20 AM Variability and inter rater reliability of ultrasound imaging of fasciae/muscles, *Carmelo Pirri, et al., Dept. Neurosciences, University of Padova, Italy*

Italy 11:40 AM Advances in imaging techniques for the study of human skeletal muscle in-vivo, *Martino Franchi, Department of Biomedical Sciences, Padua University, Italy*

Italy 12:00 AM Testosterone therapy in Alzheimer's disease, *Vittorio Emanuel Bianchi, Department of Endocrinology and Metabolism, Falciano, San Marino*

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Hotel Petrarca, Euganei Hills, (Padova), Italy

FRIDAY November 20, 2020

Virtual-Presentations: Italy Afternoon = USA Morning

Italy 1:40 PM; Iceland 0:40 PM; USA ET 7:40 AM; Japan 7:40 PM

Italy 1:40 PM **Translational Mobility Medicine Lecture 1.**

The genetic underpinning of V_{O2max} and trainability, *Hans Hoppeler, Anatomy Institute, University of Berna, Switzerland*

Italy 2:20 PM **Translational Mobility Medicine Lecture 2.**

Ear Stimulation, from Padua 1600 to cochlear implants, *Alessandro Martini, Neuroscience Department, Padua University, Italy*

Italy 3:00 PM **News on EEG, EMS, FES, TMS and more,**
Helmut Kern, Alessandro Martini, Chairs

USA ET 9:00 AM Remediating age-related cognitive and physical decline with transcranial direct current stimulation (tDCS), *Adam J. Woods, University of Florida, Gainesville, USA*

Italy 3:20 PM Characterisation of diabetic myophathy by high density EMG, *Giuseppe De Vito, CIR-Myo & Dept. Biomedical Sciences, Padua University, Italy*

Italy 3:40 PM Body mass excess, muscle mass, obesity and mitochondrial fitness, *Erich Gnaiger, Medical University of Innsbruck and Oroboros Instruments, Innsbruck, Austria*

Iceland 3:00 PM Using high density EEG to assess TMS treatment in patients with schizophrenia, *Ovidiu C Banea et al., Institute for Biomedical and Neural Engineering, Reykjavík University, Reykjavík, Iceland and Landspitali, Iceland*

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Hotel Petrarca, Euganei Hills, (Padova), Italy

FRIDAY November 20, 2020

Italy 4:20 PM; Iceland 3:20 PM; USA ET 12.00 AM; Japan 11.20 PM

Italy 4:20 PM **Therapies for genetic diseases**,
Sweeney L, Tavian D, Chairs

USA ET 10.20 AM Gene Therapies for Duchenne Muscular Dystrophy, *Lee Sweeney, Myology Institute, University of Florida, Gainesville, USA*

Italy 4:40 PM PABPN1 nuclear aggregates in oculopharyngeal muscular dystrophy, *Gillian Butler-Browne, Sorbonne Université, Paris, France*

Italy 5:00 PM Mitochondria as targets in Duchenne Muscular Dystrophy, *Paolo Bernardi, Department of Biomedical Sciences, University of Padova, Italy*

Italy 5:20 PM **Mobility Medicine Imaging**, *Feliciano Protasi, Ugo Carraro, Chairs*

Italy 5:20 PM Discovery of Calcium Entry Units: when electron microscopy still counts, *Feliciano Protasi, Chieti University, Italy*

USA ET 11.40 AM HERG Expression in C2C12 Myotubes leads to upregulation of genes related to Interferon gamma, *Amber Pond, Southern Illinois University School of Medicine, USA*

Italy 6:00 PM Formation of Tubular Aggregates in muscle: role of STIM1 and Orai1, *Simona Boncompagni, Chieti University, Italy*

Italy 6:20 PM ***Mobility Medicine, Clinical imaging**, Marco Narici, Paolo Gargiulo, Chairs*

USA WT 7.20 AM Skeletal muscle mechanics in the aging muscle: Advanced Fast MRI technologies provide insights into skeletal muscle dynamics and physiology, *Shantanu Sinha, University of California at San Diego, CA, USA*

USA WT 7.40 AM Bye, Bye Biopsy: Extracting muscle tissue composition and microstructure from Magnetic Resonance Imaging (MRI), initial validation to biopsy, and application to the aging muscle, *Usha Sinha, San Diego State University, San Diego, CA, USA*

Italy 7:00 PM Biomarkers of muscle atrophy and of neuromuscular maladaptation during 10-day bed rest. *Marco Narici, CIR-Myo, Department of Biomedical Sciences, Padua University, Italy*

Iceland 6:20 PM Predicting cardiovascular pathophysiology from a mid-thigh CT image, *Paolo Gargiulo, et al., Biomedical and Neural Engineering, Reykjavík University, Iceland*

USA ET 3:40 PM Soft tissue radiodensity, self-reported physical activity, and lower extremity function in the AGES-Reykjavík study, *Kyle Edmunds et al., Reykjavík University, Iceland*

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Hotel Petrarca, Euganei Hills, (Padova), Italy

SATURDAY November 21, 2020

Italy 9:00 ***The Center of Active Aging*** *- Helmut Kern, Chair*

9:00 AM Research in rehabilitation, past & future programs, *Helmut Kern, Wien, Austria*

9:20 AM Centre of Active Ageing: Current status, *Stefan Loefler, Wien, Austria.*

9:40 AM 15 years of Vienna-Padova-Chieti collaboration: what did we learn, *Feliciano Protasi, University of Chieti, Italy*

10:00 AM Signals from the niche to modulate muscle regeneration, *Antonio Musarò, Sapienza University of Rome, Italy*

10:20 AM Resistance training as supplemetal therapy in hypogonadal men, *Milan Sedliak, Comenius University, Bratislava, Slovakia*

10:40 AM Evaluation of sympathetic arousal by skin conductance measurement: A tool to optimize rehabilitation strategies? *Manfred Bijak, Center for Medical Physics and Biomedical Engineering, MedUni Vienna, Austria*

11:00 AM **The Center of Active** Aging – *Brainstorming on the Future*

Hans Oppeler, Lars Larsson, Chairs

Discussants: *Mauro Alaibac, Giovanna Albertin, Simona Boncompagni, Ugo Carraro, Jan Cvecka, Dusan Hamar, Cristian Hofer, Helmut Kern, Stefan Loefler, Antonio Musarò, Feliciano Protasi, Barbara Ravara, Nejc Sarabon, Sascha Sajer, Milan Sedliak, Veronika Tirpakova, Sandra Zampieri, Attendees ...*

12:30 AM **Translational Mobility Medicine Lecture 3**.

Neurogenic vs. myogenic origin of acquired muscle paralysis in ICU patients: Evaluation of different diagnostic methods

Lars Larsson, Karolinska Institutet, Stockholm, Sweden

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Hotel Petrarca, Euganei Hills, (Padova), Italy

SATURDAY November 21, 2020

2:00 PM ***Mobility Disorders & Rehabilitation I****, D Coletti, G Fanò, Chairs*

2:00 PM Treatment of Central Core Disease with Functional Electrical Stimulation (FES): a Case Report, *Feliciano Protasi, University of Chieti, Italy*

2:20 PM Modulation of some vital functions in a patient with angina pectoris using transcutaneous auricular nerve stimulation*, Janez Rozman, et al, University of Ljubljana, Slovenia*

2:40 PM Medical Emergency in critical environment: Physical capacities of Emergency Team, *Francesco Coscia, Paola V. Gigliotti, Rezhna Adil Rasheed, Giorgio Fanò-Illic, Perugia, Italy*

3:00 PM Sensitivity of the fasciae to endocannabinoid system and remodeling of fascial matrix: consequences for fascial fibrosis and inflammation, *Caterina Fede et al., Dept. Neurosciences, University of Padova, Italy*

3:20 PM Comparison of reflex period in pendulum test done in SCI and Stroke patients, *Thordur Helgason et al., Reykjavík University, Iceland*

3:40 PM Skin and mouth fluids analyses to evaluate biological age in older and oldest persons, *Giovanna Albertin et al., Dept. Neuroscience, University of Padova, Italy*

4:30 PM ***Mobility Disorders & Rehabilitation II*** *C Angelini, S Masiero, Chairs*

4:30 PM Central Myonuclei and denervation markers in Cancer Cachexia, *Dario Coletti, Sapienza University of Rome, Italy*

5.00 PM Comparison of morphological and serological analyses of denervation biomarkers in skeletal muscle wasting conditions, *Sandra Zampieri, DiSCOG, University of Padova, Italy and Austria*

5:00 PM Muscle activity prevents the uncoupling of mitochondria from Ca2+ release units induced by ageing and disuse, *Laura Pietrangelo et al., Chieti University, Italy*

5:20 PM Circulating microRNAs as promising biomarkers for monitoring of NLSDM clinical phenotype, *Valentina Pegoraro, Roberta Marozzo, Sara Missaglia, Daniela Tavian, Corrado Angelini, Padova Venice, Milan, Italy*

5:40 PM Exercise-activated $Ca2^{+}$ entry and enhanced risk of Heat Stroke. *Barbara Girolami, et al. University G. d'Annunzio of Chieti-Pescara, Chieti, Italy*

6.00 PM Methods to monitor mitochondrial activity in skeletal muscle, *Gaia Gheradi, et al., Department of Biomedical Sciences, University of Padova, Italy*

6:20 PM **Zipora Yablonka-Reuveni, Ugo Carraro: See you to 2021 (Virtual) Padua Muscle & Mobility Medicine Days (2021 V-PM3Ds), March 25-27 - Euganei Hills (Padova), Italy**

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2020 Virtual PMDs 19-21 Nov: New entries

1. November 19, 2020 – Italy Time 10.30 AM

The DLK1-DIO3 cluster miRNAs regulate mitochondrial functions in the dystrophic muscle in DMD

Ai Vu Hong (1), Nathalie Bourg (1), Peggy Sanatine (1), Jerome Poupiot (1), Karine Charton (1), Evelyne Gicquel (1), Marco Spinazzi (2), Isabelle Richard (1), David Israeli (1)*

(1) Genethon, INSREM U951, Evry, France; (2) Centre de Référence des Maladies Neuromusculaires, Service de Neurologie, Centre Hospitalier Universitaire d' Angers, France

*David Israeli: Israeli@genethon.fr

Duchenne Muscular Dystrophy (DMD) is a muscle disease which is caused by the lack of dystrophin expression. MicroRNA profiling in DMD patients and animal models revealed a coordinated dysregulation of clustered miRNAs of the DLK1-DIO3 locus (DD-miRNAs), in both serum and muscles.[1,2]. DD-miRNA dysregulation was controled epigenetically by DNA and histone methylation of key regulatory elements. A bioinformatics analysis predicted that DD-miRNAs may regulate mitochondrial functions. Indeed coinsedently with DD-miRNA dysregulation, we observed mitochondrial perturbations in the dystrophic muscles. In vivo overexpression of DD-miRNAs in healthy muscles recapitulated these mitochondrial perturbation. Thus, the present study provide evidences for a novel mechanism of mitochondrial dysfunction in DMD

Keywords: Duchen muscular dystrophy; DLK1-DIO3 ; miRNA; Mitochondrial dysfunction; Oxidative phosphorylation

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2. *Sanson M, Vu Hong A, Massourides E, et al. miR-379 links glucocorticoid treatment with mitochondrial response in Duchenne muscular dystrophy. Sci Rep 2020;10:9139. doi: 10.1038/s41598-020-66016-7*

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2. November 20, 2020 – Italy Time 11.40 AM

Testosterone therapy in Alzheimer's disease

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Alzheimer's disease (AD) is the neurodegenerative disease responsible of the most common form of dementia. Abnormal amyloid-b (Aβ) deposition induces the amyloid plaques formation and consequent degeneration of neurons in the hippocampus, amygdala, and diencephalon. Etiopathology of AD is multifactorial including genetic factors, malnutrition, and diabetes.[1] Aging is most important factor in the development of AD, however, sex hormones are largely involved in AD formation. Both 17β-oestradiol and testosterone (Te) exert a protective function on neuron against AD development regulating the Aβ production, transport, and clearance from the brain. In elderly men a low serum Te levels is correlated with a high risk of Alzheimer's disease, while a higher serum level of free Te in males and females plays a protective effect against AD development. In the present study we search systematically the RCT (randomized clinical trials) from year 2000 until now, who investigated the effect of Te on AD and cognitive impairment. We found seventeen RCT reported. The overall studies found that Te therapy improved cognition and memory, however a few did not find any improvement, other a modest improvement of cognition.[2] One study found a detrimental effect of Te administration on verbal memory and in median and prefrontal activity, but no test on cognition were done.[3] Discrepancies between the studies are due to the different clinical methodology of investigation, time duration of therapy (small number of patients, clinical investigation of dementia, other pathologies as confounding factors). However, the most relevant drawbacks are related to the lacking of determination other hormones, largely involved in the neurotrophic process, such as 17β-estradiol and IGF-1 that are hormones. Further studies with a strong methology are necessary to evaluate the effect of Te in AD therapy.

Keywords: Testosterone therapy, Alzheimer's disease, review.

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3. November 20, 2020 – Italy Time 1.40 PM

Translational Lecture 1. The genetic underpinning of V_{O2max} and trainability

Hans Hoppeler

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Maximal oxygen consumption (V̇ O2max) denotes the reproducible upper limit of oxygen (energy) flux through the respiratory system into skeletal muscle mitochondria that canbe reached during intense exercise with a large muscle mass. A high $\dot{V}_{O2}$max is a key requisite for success in all endurance sports such as cycling, cross-country skiing or running over longer distances. However, $\dot{V}_{O2}$max has also been strongly and negatively associated with cardiovascular diseases and all-cause mortality. $\dot{V}_{O2}$max can vary by more than twofold between untrained, sedentary subjects with a heritability value greater than 50%.[1] Trainability for an individual's $\dot{V}_{O2}$max also varies massively between subjects. Trainability is independent of sedentary $\dot{V}_{O2}$max with a similarly high heritability as sedentary $\dot{V}_{O2}$max.[2] The high heritability of sedentary $\dot{V}_{O2}$max and trainability and its importance for athletic performance as well as health has prompted a massive search for its genetic underpinning. Candidate-gene studies, gene-expression studies and genome-wide-association studies (GWAS) have failed to identify a genetic signature of the high $\dot{V}_{O2}$max phenotype.[3] This may be due to the fact that there are vast multigenetic regulatory networks in skeletal muscle and in other organs that are responsible both for the set-point and the malleability of $\dot{V}_{O2}$max. Multigenetic phenotypes such as $\dot{V}_{O2}$max appear to be emergent properties of multiple underlying transcriptomic networks modified by epistasis, the epigenome and the epitranscriptome. This situation is very similar to the situation of the biological organisation of the immunodefence in COVID 19. It is postualted that the wide variability of the susceptibility to COVID 19 is based on a very similar condition and currently defies characterisation. It is unclear whether an artificial intelligence approach on sufficiently large datasets can make reliable predictions on multigenetic phenotypes such as $\dot{V}_{O2}$max.

Keywords: endurance, exercise, health, epigenetics

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4. November 20, 2020 - USA ET 3:40 PM

Soft tissue radiodensity, self-reported physical activity, and lower extremity function in the AGES-Reykjavík study

Kyle J. Emunds (1,2,3)*, Ozioma C. Okonkwo (1,2,3), Sigurdur Sigurdsson (4), Sarah R. Lose (1,2,3)Vilmundur Gudnason (4,5), Ugo Carraro (6,7), Paolo Gargiulo (8,9)

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While prior studies have highlighted associations between physical activity (PA) and lower extremity function (LEF) in the elderly,[1] the mechanisms underlying this relationship remain debated.[2] Our recent work has realized the quantitative potential of nonlinear trimodal regression analysis (NTRA) parameters in characterizing soft tissue radiodensity changes and their relationship with sarcopenia and aging health in the population-based AGES-Reykjavík study.[3-5] For the present investigation, a series of prospective multivariate regression models were assembled to interrogate whether these soft tissue NTRA parameters mediate the longitudinal relationship between PA and LEF in AGES-Reykjavík. Elderly volunteer subjects from AGES-Reykjavík underwent Computed Tomography (CT) scans and a battery of four LEF tasks: normal and fastest-comfortable gait speed, timed up-and-go, and isometric leg strength. These data were recorded at two study timepoints separated by approximately five years: AGES-I (n = 3,157) and AGES-II (n = 3,098). AGES-I participants were also given a questionnaire to self-report their frequency of weekly moderate–vigorous PA (PAAGES-I). Covariate-adjusted multivariate multiple regression models were assembled under a mediation analysis framework to test whether NTRA parameters mediated the relationship between PAAGES-I and

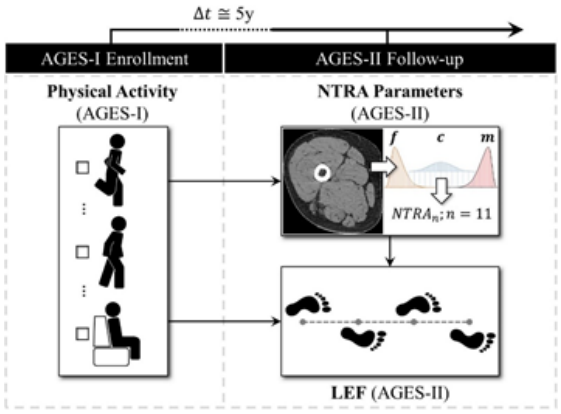

Fig 1. *Graphical summary of the present work, showing the theorized role of NTRA mediators on the five-year longitudinal relationship between self-reported physical activity and LEF.*

LEFAGES-II. Models of the five-year longitudinal relationship between PAAGES-I and LEFAGES-II indicated that all four LEF tasks were significantly related to PAAGES-I after adjusting for covariates and controlling for multiple statistical comparisons. Modelling the relationship between PAAGES-I and NTRAAGES-II parameters as theorized mediators indicated muscle amplitude (Nm) and location (μm) as potential mediators of LEF. Finally, adding these two parameters to prior PAAGES-I→LEFAGES-II models resulted in the attenuation of PAAGES-I β coefficients, and bootstrapping confirmed Nm and μm as significant partial mediators. This work altogether presents a novel approach toward clarifying the nature of the relationship between PA and LEF in aging populations. In particular, the identification of Nm and μm as significant partial mediators of the longitudinal relationship between PAAGES-I and LEFAGES-II is strong evidence that PA promotes mobility in aging through the preservation of skeletal muscle quantity and quality.

Keywords: Computed Tomography, Sarcopenia, Physical Activity, Lower Extremity Function, AGES-Reykjavík study.

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5. November 21, 2020 – Italy Time 12:00 AM

Neurogenic vs. myogenic origin of acquired muscle paralysis in intensive care unit (ICU) patients: Evaluation of different diagnostic methods

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The aquired muscle paralysis associated with modern critical care can be of neurogenic or myogenic origin, yet the distinction of between these origins is hampered by the precision of current diagnostic methods. This has resulted into the pooling of all acquired muscle paralyses, independent on origin into the term Intensive Care Unit Acquired Muscle Weakness (ICUAW). This is unfortunate since the acquired neuropathy (Critical Illness Polyneuropathy, CIP) has slower recovery than the myopathy (Critical Illness Myopathy, CIM), therapies need to target underlying mechanisms and every patient deserves as accurate diagnosis as possible.[1] This study aims at evaluating different diagnostic methods in the diagnosis of CIP and CIM in critically ill, immobilized and mechanically ventilated intensive care

unit (ICU) patients. ICU patients with acquired quadriplegia in responmse to critical care were included in the study. A total of 142 patients were examined with routine electrophysiological methods, together with biochemical analyses of myosin actin (M:A) ratios of muscle biopsies. In addition, the comparison of evoked EMG response in direct vs. indirect muscle stimulation and histopathological analyses of muscle biopsies were performed in a subset of the patients. ICU patients with quadriplegia were stratified into five groups based on the hallmark of CIM, i.e., preferential myosin loss (myosin:actin ratio, M:A) and classified as severe (M:A< 0.5; n= 12), moderate (0.5≤M:A<1; n= 40), mildly moderate (1≤M:A<1.5; n=49), mild (1.5≤M:A<1.7; n= 24) and normal (1.7≤M:A; n=19). Identical M:A ratios were obtained in the small (4-15 mg) muscle samples using a disposable semiautomatic microbiopsy needle instrument as in the larger (>80 mg) samples obtained with a conchotome instrument. Compound muscle action potential (CMAP) duration was increased and amplitude decreased in patients with preferential myosin loss but deviations from this relationship were observed in numerous patients resulting in only weak correlations between CMAP properties and M:A. Advaned electrophysiological methods measuring refractoriness and comparing CMAP amplitude after indirect nerve vs. direct muscle stimulation are time consuming and did not increase precision compared with conventional electrophysiological measurements in the diagnosis of CIM. Low CMAP amplitude upon indirect vs direct stimulation strongly suggests a neurogenic lesion, i.e., CIP, but this was rarely observed among the patients in this study. Histopathological diagnosis of CIM/CIP based on enzyme-histochemical mATPase stainings were hampered by poor quantitive precision of myosin loss and the impact of pathological findings unrelated to the acute quadriplegia. Conventional electrophysiological methods are valuable in identifying a peripheral origin of quadriplegia in ICU patients, but do not reliably separate between neurogenic vs. myogenic origin of paralysis. The hallmark of CIM, the preferential myosin loss, can be reliable evaluated in the small samples obtained with the microbiopsy instrument. The major advantage of this method is that it is less invasive than conventional muscle biopsies, reducing the risk of bleeding in ICU patients frequenly on anticoagulantia treatment, and it can be repeated multiple times during follow up for monitoring purposes.

Keywords: Critical care, myosin, myopathy, ENeG, EMG, CMAP, muscle biopsy

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6. November 21, 2020 – Italy Time 3:00 PM

Central Myonuclei and denervation markers in Cancer Cachexia

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An idiopathic myopathy characterized by central nuclei in muscle fibers, a hallmark of muscle regeneration, has been observed in cancer patients. In cancer cachexia skeletal muscle is incapable of regeneration, consequently, this observation remains unaccounted for. In C26-tumor bearing, cachectic mice, we observed muscle fibers with central nuclei in the absence of molecular markers of bona fide regeneration. These clustered, non-peripheral nuclei were present in NCAM-expressing muscle fibers. Since NCAM expression is upregulated in denervated myofibers, we searched for additional makers of denervation, including AchRs, MUSK, and HDAC. This last one being also consistently upregulated in cachectic muscles, correlated with an increase of central myonuclei. This held true in the musculature of patients suffering from gastrointestinal cancer, where a progressive increase in the number of

central myonuclei was observed in weight stable and in cachectic patients, compared to healthy subjects. Based on all of the above, the presence of central myonuclei in cancer patients and animal models of cachexia is consistent with motor neuron loss or neuromuscular junction perturbation and could underlie a previously neglected phenomenon of denervation, rather than representing myofiber damage and regeneration in cachexia. Similarly to aging, denervation-dependent myofiber atrophy could contribute to muscle wasting in cancer cachexia..

Keywords: Central Myonuclei, denervation markers, cancer cachexia

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7. November 21, 2020 – Italy Time 6:40 PM

Exercise-activated Ca2+ entry and enhanced risk of Heat Stroke

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Exertional/Environmental Heat Strokes (EHSs) are hyperthermic crises triggered by strenuous physical exercise and/or exposure to environmental heat, which are caused by an altered intracellular Ca2+ homeostasis in muscle (Bouchama and Knochel, 2002).[1] Store-Operated Ca2+ Entry (SOCE) is a mechanism that influences intracellular Ca2+ levels, allowing recovery of extracellular Ca2+ during prolonged activity. We recently demonstrated that exercise leads to formation of Calcium Entry Units (CEUs), intracellular junctions between stacks of sarcoplasmic reticulum (SR) and transverse tubules (TTs) at the I band that promote interaction between STIM1 and Orai1, the two proteins that mediate SOCE (Boncompagni et al. 2017; Protasi et al. 2020).[2,3] Here we tested the hypothesis that exercise-induced assembly of CEUs may increase the risk of hyperthermic crisis when physical activity is performed in challenging environmental conditions. 4 months old mice were: a) first, divided in 3 experimental groups: control, trained-1m (1 month of voluntary running in wheel cages), and exercised-1h (1 hour of incremental treadmill run); and b) second, subjected to an incremental treadmill run of 45 min at 34°C and 40% humidity. We then: a) measured the internal temperature of mice, which was higher in the pre-exercised groups (trained-1m: 38.9°C ± 0.33; exercised-1h: 38.7°C ± 0.40) compared to control (37.9°C ± 0.17). b) applied an ex-vivo exertional stress protocol to isolated EDL muscles (tetanic stimulation performed at 30°C) and verified that samples from trained-1m and exercised-1h mice generated a tension significantly greater than control. c) Analyzed CEUs by electron microscopy (EM) and verified that EDL muscles of exercised-1h ad trained-1m mice contained a greater number of elements forming CEUs. The data collected suggest that assembly of Calcium Entry Units during exercise could predispose to EHS when exercise is performed in challenging environmental conditions.

Keywords: Exercise-activated $Ca2^+$ entry, risk of heat stroke, challenging environmental conditions

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List of acronyms

AD - Alzheimer's disease
CEUs - Calcium Entry Units
CIM - Critical Illness Myopathy

CIP - Critical Illness Polyneuropathy
CMAP - Compound muscle action potential
COVID - Coronavirus COVID-19 outbreak
DMD - Duchenne Muscular Dystrophy
EHSs - Exertional/Environmental Heat Strokes
EJTM – European Journal Translational Myology
GWAS - genome-wide-association studies
ICU - intensive care unit
ICUAW - Intensive Care Unit Acquired Muscle Weakness
LEF - lower extremity function
NTRA - nonlinear trimodal regression analysis
PA - physical activity
PMDs – Padua Muscle Days
SOCE - Store-Operated Ca2+ Entry
SR - sarcoplasmic reticulum
Te – testosterone
TTs - transverse tubules
PM3Ds - Padua Muscle & Mobility Medicine Days

Acknowledgments

The authors thank Attendees for supporting the postpone 2020 Virtual PMDs to 19-21 November, 2020.

Funding

E-publishing of this typescript is supported by the Armando & Carmela Mioni-Carraro Foundation for Translational Myology Padova, Italy and by PAGEpress, Pavia, Italy. The 2020 Virtual PMDs events are supported by Osato Research Institue, Gifu, Japan, OROBOROS, Insbruck, Austria, Physiko- & Rheuma-therapie, Institute for Physical Medicine and Rehabilitation, St. Pölten, Austria, Centre of Active Ageing—Competence Centre for Health, Prevention and Active Ageing, St. Pölten, Austria and Ludwig Boltzmann Institute for Rehabilitation Research, St. Pölten, Austria.

Conflict of Interest None.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Submitted: October 27, 2020
Accepted for publication: October 30, 2020