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Department of Biomedical Sciences

2013 Spring Padua Muscle Days

Ludwig Boltzmann Institute
Electrical Stimulation and Physical Rehabilitation

Padua (Italy), May 2, 2013

PalaFellin VS-03 Conference Hall, Padua University Hospital, Via Giustiniani 2, Padova, Italy

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Organizers: H. Kern, S. Masiero, F. Bassetto, U. Carraro

Thursday May 2, 2013

Padova University Hospital, Via Giustiniani 2, Padova, Italy

PalaFellin VS-03 Conference Hall

10.00 **Interreg IVa "Mobility in elderly"** – Partner meeting – *Helmut Kern, Ugo Carraro, Chairmen*

13.50 **Openings - Stefano Masiero, Franco Bassetto, Ugo Carraro**

14.00 MED EL Lecture

Neural Injury and regeneration: accelerating axon growth after peripheral nerve injury

Tessa Gordon

Department of Surgery, Plastic Reconstructive Surgery, The Hospital for Sick Children, Toronto, Canada

15.00 ***Electrical Stimulation of Skeletal Muscle*** *– H. Kern, U. Carraro, Chairmen*

15.00 Interreg IVa "Mobility in elderly": Rehabilitation studies in denervation, aging and oncology, *S. Zampieri, H. Kern, University of Padua, Italy and LBI, Wien, Austria*

15.15 Lifelong high physical activity delays aging muscle decline by increasing reinnervation, *S. Mosole et al., University of Padua, Italy and LBI, Wien, Austria*

15.30 Age-related decline of skeletal muscle power in master athletes, *P. Gava, et al., University of Padua, Italy and LBI, Wien, Austria*

16.00 Total count of muscle myofibers and motor units in aging, *U. Carraro et al. University of Padua, LBI, Wien, Austria and Landspitaly Hospital, Reykjavik, Iceland*

16.15 ES in neural repair: first experience in Vienna, *M. Mödlin, LBI, Wien, Austria*

16.30 Epidemiology of traumatic arm denervation in Padua, *L. Masetto et al., Padova, Italy*

16.45 Steps toward a walking aid for denervated tibialis anterior, *A. Marcante, et al., Padova, Italy*

17.00 Exercise therapy in Amiotrophic Lateral Sclerosis, *A. Merico, et al., San Camillo H., Venice, Italy*

17.15 ***General Discussion***

17.45 Adjö, Arrivederci, Auf Wiedersehen, Aurevoir, Búcsú, Despedida, Poslovite, Sjámst, See You to the 2013Autumn PaduaMuscleDays, Terme Euganee, November 14-16, 2013, *Ugo Carraro*

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Abstracts

Editorial

2013Spring PaduaMuscleDays, May 2, 2013 Massimiliano Aloisi Legacy

Massimiliano Aloisi departure on October 22, 1999 took away a model for biomedical students and scientists, leaving an indelible sorrow for many in Pathology, Neurosciences and Italian Universities. He was known for his studies on damage and muscle regeneration after Vitamin E deprivation and supplementation. Those studies developed into an Italian-US collaboration in the 60s of last century, obtained founds from the Muscle Dystrophy Association of America and opened to his young fellows the doors of many International Laboratories and Universities. Some of his students returned to Italy with precious knowledge, others succeeded to became Professor of Neurology and Myology Leaders in the States. Other pupils succeeded as brave and innovative surgeons. Massimiliano Aloisi had also strong friendly relationships with East-Europe Scientists, and managed to help them when in troubles for their political choices. One of his main roles was to encourage the development of culture systems for muscle cells (in vivo and in vitro). Furthermore, he opened in Padua a muscle Electron Microscopy laboratory with many good fellows. Charismatic, and often controversial, he was Professor of General Pathology in Ferrara, Modena and Padua, but maintained for all his life his Roman roots, participating to the Italian National Research Council (C.N.R.) organization and management. We remember the three goals of his life: i) Promotion of the scientific method and of "the scientific Systems Medicine", ii) Internationalization of research, and iii) Strong mentorship of young students and scientists. Proud of his Roman roots and of being a Professor in one of the University in which Galileo Galilei taught and the Normal Anatomy and Medical Pathology had been developed, he was a fascinating "Maestro". Some of his pupils, which are here present, remind his presentations of histopathological cases by projecting his own beautiful color slides. He always taught raising questions and patiently driving to replies a crowd of students. His Socratic teaching influenced many young Italian doctors, not enough, unfortunately, considering the bad decisions that the majority of them took in "reforming" the Italian Medical School during recent years! The University of Padua is proud to honor the memory of one of his Professors, sponsoring the Meeting on "Skeletal muscle in denervation, aging and cancer, Padova and Terme Euganee, Padua (Italy), March 15 – 17 and May 2, 2013". Many experts in muscle damage and functional recovery are participating, in particular those fond of rehabilitating paraplegics by FES, but other world-class experts in Cell Stemness for the recovery of muscle and other soft tissues are among Lectures and Speakers. Padua is notoriously a city of great cultural prestige. Thanks to its ancient University, it has been a landmark for arts, philosophy, law, medicine and science during the centuries. Testimonies of its prestigious past remain also near us. You may today visit the anatomical theatre where Fabrizio d'Aquapendente performed the first autopsies with scientific spirit and where five hundreds years ago William Harvey discovered how the heart pumps blood toward the body. Chair of Galileo Galilei, the great supporter of the experimental method, is over the next door. In the past, and today, great personalities (painters, among others) converged in Padua. The Scovegni's Chapel, painted by Giotto, is a Renaissance's jewel.We would like to remind and witness to people, who did not meet Massimiliano Aloisi, his enthusiasm for research, his pragmatism and perseverance to overcome difficulties, and above all his high motivation as a fundamental message for young generations.

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Neural injury and regeneration
Accelerating axon growth after nerve injury

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Axons in the peripheral nervous system (PNS) conduct action potentials from one node of Ranvier to another, the myelin sheath formed by Schwann cells insulating the axons between the nodes. Accelerated conduction velocity due to the nodal conduction is also a feature of myelinated axons in the central nervous system (CNS) where the oligodendrocytic glial cells enwrap several axons to form myelin sheaths. After nerve injuries that disrupt axon continuity, the axons that are disconnected from their cell bodies undergo Wallerian degeneration with dissolution of the axons and their myelin sheath. The glial cells multiply but it is only the Schwann cells in the PNS that support the outgrowth and elongation of regenerating axons, the myelin products of the oligodendrocytes inhibiting axon growth in the CNS. The expression of growth associated genes in the cell bodies of injured peripheral nerves and the Schwann cells in the growth pathway facilitate axon outgrowth and regeneration within the distal nerve pathway after surgical apposition of the proximal and distal nerve stumps. Axons regenerate at the rate of slow axon transport, the rate being 1-3mm per day. However, there are substantial delays and asynchronous outgrowth of axons at the injury site. The Schwann cells and extracellular matrix are initially disorganized at this site before they gradually form Bands of Bungner of longitudinally orientated Schwann cells that extend throughout the endoneurial tubes that previously surrounded each axon in the distal nerve pathway. The Schwann cells are critical for axon regeneration, their presence and guidance being essential for axon regeneration to occur. At the time of nerve repair, a brief period of one hour low frequency electrical stimulation is sufficient to dramatically accelerate the outgrowth of axons across the injury site of surgically repaired peripheral nerves. As a result, the more synchronous outgrowth of axons results in accelerated regeneration through distal nerve stumps and their earlier reinnervation of denervated targets. Although the electrical stimulation does not accelerate the rate of axon regeneration once the axons reach the distal nerve stump, the accelerated axon outgrowth is functionally significant in the light of the transient expression of growth associated genes in the injured neurons that have not yet regenerated their axons to make functional target connections with associated progressive decay in their regenerative capacity. The growth supportive Schwann cell phenotype is also time-limited such that their expression of their growth supportive genes declines with time such that they cannot support the regeneration of axons through the long distal nerve pathways at the relatively slow rate of axon regeneration. The accelerated axon outgrowth is associated with increased levels of neuronal cAMP and expression of the growth associated genes in the injured neurons. The transient expression has recently been shown to be prolonged by administration of anabolic steroids such that both when combined with brief periods of electrical stimulation, axon outgrowth and rate of regeneration are both accelerated. These findings in animal studies are very promising and proof of principle studies in human nerve injuries demonstrate dramatic increase and accelerated functional recovery.

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Interreg IVa "Mobility in elderly"
Rehabilitation studies in denervation, aging and oncology

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During the last decade, we contributed to study rehabilitation strategies for degenerating skeletal muscles in different pathologic conditions of permanent denervation, aging, and more recently, cancer. We focused on the role of physical exercise induced by Functional Electrical Stimulation (FES) to rehabilitate skeletal muscles in the special case of Spinal Cord Injury (SCI) patients affected with complete injury of the Conus Cauda, a syndrome in which the denervated leg muscles are fully disconnected from the nervous system, inducing ultra structural disorganization of the affected skeletal muscles within a few months from SCI, and resulting in severe atrophy with nuclear clumping and fibro-fatty degeneration within 3 and 6 years from lesion, respectively [1-4]. To counteract these progressive changes, a novel home-based (h-b) therapy concept for paraplegic patients was developed by means of new electrodes and a safe stimulator

which is able to elicit contractions of denervated skeletal muscle fibers in absence of the nerves [5,6]. In parallel, specific clinical assessments and trainings were developed [7], based on sound evidence from animal experiments [8]. The study demonstrated that h-b FES of permanent denervated muscle is an effective home therapy that results in the rescue of muscle mass, function and perfusion [9-12]. We are now extending our studies on h-b FES application to the larger cohort of elderly, in order to assess the effects of exercise on aging rehabilitation. We are analyzing at microscopic, ultrastructural and molecular levels quadriceps muscle biopsies from young (23 years) [13] and senior male subjects: sedentary elderly and senior sportsmen (a peculiar group of subjects that performed life-long sport activities) with a mean age of 70 years. Two protocols of 10 weeks training strategies (leg press or electrical stimulation) were applied to the group of sedentary seniors and the analyses performed before and after the training period. Preliminary results confirm the effectiveness of h-b FES, and the importance of physical exercise, on age related decay of skeletal muscle, also counteracting denervation atrophy by promoting reinnervation. More recently, based on our original observation of a subclinical myopathy in patients affected with newly diagnosed colorectal cancer, therefore at the very early stage of disease [14,15], we are now extending our approaches to oncologic rehabilitation. Cancer-related skeletal muscle wasting has profound effects on functional outcomes and quality of life. Evidences from recent publications indicate that repeated exercise may enhance the quality of life of cancer patients. When started early during the progression of disease, i.e. at the stage in which the subclinical myopathy can be observed, regular physical exercise may prevent or control the progression of cancer-associated myopathy, possibly counteracting some of the mechanisms underlying muscle wasting. A comprehensive study on the potential molecular mechanisms that are responsible for this cancer-associated myopathy could possibly provide new diagnostic and prognostic markers and new therapeutic and rehabilitation targets to prevent the severe loss of muscle tissue which characterizes late-onset cancer cachexia [16-17].

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Lifelong high physical activity delays aging muscle decline by increasing reinnervation

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Although denervation has long been implicated in aging muscle, the degree to which it causes the loss of myofibers is unknown [1-3]. To address these questions, we quantified in senescent patients (either sedentary or with a life-long history of amateur sport) the percentage and size of denervated and innervated muscle fibers in a leg muscle using both in situ co-expression of fast and slow myosin heavy chain and the ATPase assay. Quantitative histological analyses show that the average diameter of skeletal muscle fibers from Vastus Lateralis is significantly higher in senior sportsmen compared to sedentary and that the proportion of severely atrophic denervated myofibers with a mean myofiber diameter < 30 □m is lower compared to those observed in sedentary elderlies. The percentage of myofibers co-expressing fast and slow MHC (and thus the possible product of exercise-induced plasticity, or denervation/reinnervation) are in young, senior sportsmen and sedentary seniors 1,4±1,42, 6±3,54 and 9,57±9,74 (mean +/- SEM), respectively. The differences are statistically significant only in the case of young vs. senior sportsmen ($p < 0.05$). Their actual percentage in the three different groups does not speak in favor of age-related or exercise-related plasticity, but of seldom events of peripheral denervation/reinnervation. Reinnervation events identified as fiber type groupings were observed in all muscle biopsies from senior sportsmen (100%), while they were detected in 60% of sedentary elderly. The total number of fiber type groupings detected in seniors sportsmen (177, of which 174 were of slow type, 98%) was significantly higher compared to that observed in sedentary seniors (39, of which 19 were of slow type, 49%).

Extent of reinnervation in skeletal muscle biopsies from 70-year sedentary seniors and senior sportsmen estimated from fiber-type groupings

	Biopsies with fiber-type grouping		Number of fiber-type grouping	
	positive (%)	negative (%)	fast type	slow type
Sedentary seniors (14) 28 biopsies (two legs)	18 (64%)	10 (36%)	20	19
Senior sportsmen (14) 28 biopsies (two legs)	28 (100%)	0	3	174

In senior sportsmen the higher prevalence of slow type fibers predominantly clustered in type groupings compared to fast type fibers suggests that the amount of endurance exercise these subjects performed lifelong, induced an increment and a strengthening of the oxidative muscle metabolism. In summary, our study provides a quantitative assessment of the contribution of denervation/reinnervation events to muscle decline in aging. A renewed focus on these aspects, in seeking for their clinical relevance and to understanding of causes and mechanisms may identify new targets for therapy/rehabilitation of aging muscles.

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Age-related decline of skeletal muscle power in master athletes

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The power developed by skeletal muscles is declining with age after the growth of the youth [1-6]. The characterization or the rate of loss is a question analyzed in many clinical research studies. Data useful to study the decline of the skeletal muscles power are largely available from sources other than medical tests, e.g. from track and field competitions of master athletes [1-3]. Absolute world records of various athletic events have been collected together with world records of all master categories. Masters are athletes competing within age classes of 5 years (39 to 39; 40 to 44; 45 to 49 and so on). The performance of master athletes can be normalized with respect to the absolute record: the normalized performances are thus represented by a number ranging from one (world absolute records) to zero (null performance). The baseline of the data (from 35 years up to 100 years) is very extended, especially in comparison with the age extension of most clinical tests. Furthermore, the data are associated with individuals with highly similar boundary conditions: athletes physically gifted for the specific performance at their best condition and top motivation. Such

uniform boundary conditions are not available in any longitudinal or (even worse) cross-sectional study. The decline of the normalized performances with age are analyzed and compared. Power decline of skeletal muscle power in all track and field events starts at the age of 30 with minor variance. This conclusion is in line only with some of previous studies. The power decline of all events tends to zero at the age of 110 years. This is substantially in line with the actual survival of humans. Most trend-lines show a linear decline down to 70 years. The annual rate of decline of analyzed events (running, throwing and jumping) ranges from a surprisingly moderate annual decline of about 0.5 for the shortest running events (60 and 100 meters) to something like 1.5 % for the throwing events (shot put and javelin throw). The power developed at 70 years in the short runs is 75 % of the power developed at 30 years; the power developed at 70 years in the throwing events is 35 % of the power developed at 30 years. Apparently during the initial 40 years of decline the power developed by the lower limbs falls with age less than the power developed by upper limbs. At 70 years the capacity of developing power of the upper limbs is declined twice (!) than the lower limbs. The situation is reversed in the second half of the decline phase, after the age of 70. Whatever the mechanisms of the different declines in power, the results have implications for prevention and rehabilitation strategies of elderly-related diseases.

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Total count of muscle myofibers and motor units in aging

Ugo Carraro (1), Helmut Kern (2), Simone Mosole (1,2), Sandra Zampieri (1,2), Riccardo Zanato (3), Roberto Stramare (3), Paolo Gargiulo (4,5)

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Although denervation has long been implicated in aging muscle, the degree to which it causes loss of myofibers is an open issue in humans, since reinnervation events may long-term compensate motor neuron loss in spinal cord and/or axonal abnormalities along peripheral nerves [1,3,9-14,16-23]. Recent experimental study in rodent provides quantitative assessment of the contribution of denervation to myofiber changes in aging muscle, suggesting that it explains the majority of the observed atrophy [18]. This striking result suggests that a renewed focus should be placed on denervation in seeking for its clinical relevance, to understand its causes and mechanisms and to validate new treatments of aging muscle atrophy. Translation of animal results to humans asks for methods to count in vivo total number of myofibers in anatomically identified muscles, thus corroborating electrophysiological evidence of loss of motor units [3,10,16]. This will be of main value in longitudinal approaches to test extent of denervation-induced loss of myofibers and its relevance in prevention and rehabilitation strategies. In collaboration with Landspitali Hospital, we are designing and planning a non-invasive approach based on Gray Value analysis [4-8], but using μCT technologies [2]. Recent reports demonstrate the feasibility to analyze and quantify micro structural changes within biological scaffolds using μCT and image processing software techniques. Our vision is to identify and count selectively single myofibers in an anatomically defined human muscle to validate 3D color computer tomography [4-8,15] as a method to identify and count single myofibers in muscles of human head, arm, hand, leg and foot, using μCT technologies [2]. As a first step we will analyze ex-vivo rodent muscles, segmenting myofiber morphometry of isolated leg muscles using the General Electric nanotom x-ray μCT system, which have up to 200 nm detail detectability. Validation of this approach may provide the final evidence to establish improved prevention/rehabilitation strategies to delay/reverse aging-related muscle changes and complications due to accompanying diseases.

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ES in neural repair: first experience in Vienna

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Encouraged by Tessa Gordon's studies on nerve regeneration [1], especially in humans, we plan to investigate the effect of electrical nerve stimulation immediately after nerve reconstruction. We will include patients with complete transection of median or ulnar nerve at the elbow or the forearm who undergo operation with sural nerve transplantation. After suture and wound dressing two small, self-adhesive electrodes will be placed at the proximal and the distal end of the incision directly over the nerve and connected to a small stimulator. The nerve will then be stimulated for one hour with continuous 20Hz stimulation with an intensity that would elicit strong tetanic contraction in the contralateral side. EMG examinations will be carried out once before the operation and every 4 weeks after the operation until the reinnervation process is completed. Main outcome measure will be the time point of the first reinnervation potentials in EMG related to the distance between the proximal nerve suture and the target muscle.

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Abstracts

Epidemiology of traumatic arm denervation in Padua

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Peripheral nerve injury can entail different disorders: strength and muscular balance deficit, sensibility deficit, sympathy function loss, pain. It results in peculiarity deficit and rigidity development, algodystrophic alteration, protection sensation deficit and then further trauma risks.
The type of trauma first of all determines management and prognosis. A sectioned nerve has no chance of spontaneous healing and discontinuity must be surgically repaired. Sprain nerve damage or significant distance between stumps have worse prognosis than clear local nerve cut. Mixed nerves have poor functional regeneration. Sensitive terminations degenerate more rapidly than motor ones. Outcome is also conditioned by general patient conditions. Young patients have better recovery. Diabetes, cardiovascular, immunity and other systemic disease can complicate the procedure.
In our Operative Unit of Plastic and Hand Surgery in the last three year 78 neurorrhaphy were performed. Just 2 patients were submitted to a secondary repair of a great segmental loss with graft. 76 procedures were executed in urgency room, until 3 hours after the trauma. 62 were performed on digital nerves and 14 on forearm nerves. Then all the patients followed up for 15 days to 2 year. Surgical repair consisted in the suture of the ends of the nerve. Early repair is the first choice, if permitted by a clean wound and no nerve segmental loss, because extensive nerve retraction has not occurred yet. Otherwise a delayed primary repair can be performed within 14 days. Secondary repair, two weeks after until 2 years after injury, is still indicated but achievement decrease with delay. Neurorrhaphy is executed by micro sutures carried out around epineurium, to accomplish group fascicular repair or every single fascicle through the perineurium and it is performed after aligning the nerve ends according to fascicular pattern and epineurial landmarks. Reconstruction after peripheral nerve injury may require management of segmental defects in the damaged nerve. Donor nerve for grafting is usually patient sural nerve.
Regeneration of peripheral nerves is remarkably restrained across transection injuries, limiting recovery of function. Strategies to reverse this common and unfortunate outcome are limited. Remarkably, however, new evidence suggests that a brief extracellular electrical stimulation (ES), delivered at the time of injury, improves the regrowth of motor and sensory axons [2]. Further reports describe positive effects of electrical stimulation on repair of peripheral nerve injuries either in experimental or clinical settings [1-6]. Our Operative Unit will test early electrical neurostimulation, as described in [2-5], on patients undergoing early digital neurorrhaphy.

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Steps toward a walking aid for denervated tibialis anterior

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Electro stimulation of denervated muscle is still a controversial issue with lack of clinical studies based on patients with peripheral nerve lesions. We report on a case of a 26 years old man with a complete sciatic nerve injury related to a subtrochanteric fracture of the right femur caused by car accident in 2010. Femur fracture was correctly fixed with a long gamma nail but clinically, patient has still presented a complete anesthesia under his right knee and some pain on the gluteal region. The strength of the hamstrings was almost spared, but flexion and extension of the ankle were impossible, with a severe impaired deambulation. In 2011 the patient underwent a surgery of neurolysis with removal of a voluminous neuroma and positioning of an 8 cm controlateral sural nerve graft. One year after the surgery the patient refers disappearance of gluteal pain, strengthening of the hamstrings but no improvement in the muscles of the shank, so we decided to perform an electro stimulation test to verify the response of tibia is anterior and triceps surae muscles. Using a Neuroton (Philips) stimulator, we applied a current of 10 to 30 mA with triangular monophasic waves, impulse length from 5 to

150 msec with a pause of 1 or 2 sec. The best muscular response with no pain for the patient was evident with a 20-25 mA current, impulse length of 150 msec and pause for 2 seconds. At home, the patient applied similar electrostimulation parameters using the electrostimulator SM1 (Demitalia, Medical Technology S.r.L., Torino, Italy) with the schedule: 2 sessions (lasting 30 minutes each) per day for the first month, then 5 sessions per week. After two months, the electrostimulation test revealed muscle contraction also with a 50 msec impulse length using a current of 25 mA. The denervated TA (at more than 1 year from sciatic nerve lesion and attempted surgical reconstruction) responded with twitches to adequate surface stimulation. Two months of "adequate stimulation" (150 msec Impulse Duration (ID), 25 mA) recovered excitability up to the point that a "tetanizing" protocol may be attained, despite the fact that the twitch-training did not hampered the process of atrophy or improved kinetics of contraction/relaxation of the twitch induced by home-based surface Functional Electrical Stimulation (h-b FES). The next step in the process of functional recovery will be to recover mass and force of TA with a "tetanizing" training (series of impulse trains of 2-3 second duration at intervals of 3 sec) against increasing resistance to dorsiflexion of the foot (by acting a "spring device" opposing foot dorsiflexion). In conclusion the patient improved in two months of twitch-stimulation so much the excitability of the persistently denervated tibialis anterior that a tetanizing protocol, with its therapeutic potential to be used in a "walking aid for denervated muscle", would be the next "step" in the rehabilitation program.

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Exercise therapy in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal and progressive neurodegenerative ddisorder affecting motor neurons. If the reduced level of activity persists, cardiovascular deconditioning and disuse atrophy superimpose on weakness and muscle atrophy caused by the ALS itself [1]. The animal studies provided good basic scientific information about the effects of endurance exercise training in terms of survival and of reduction of the degeneration of the motor neurons in mice with SOD-1 induced ALS [2, 3]. In other studies, the neurons controlling fast fibres were noted to degenerate early in the course of ALS, whereas fatigue resistant neurons failed in the intermediate and slow twitch neurons in the later stages [3]. In the isometric muscular contraction, the force applied by the muscle is not sufficient to move the load, and as a result, the muscle does not shorten though its muscle tension or force of contraction increases [4]. Therefore, an isometric contraction should be proposed in order to avoid both the overuse weakness muscle and overstressing the twitch muscle fibres. In addition, moderate endurance training has been developed in order to minimize the fatigue, to facilitate the musculoskeletal endurance and to enhance the cardiopulmonary efficiency. Previous studies suggest an early subclinical involvement of the autonomic system in ALS [5]. The depressed sinus arrhythmia observed in no bulbar patients might be the result of a decreased state of physical condition resulting by a deconditioning. Bulbar patients, instead, show a more severe autonomic dysfunction than no bulbar patients. Several clinical trials have demonstrated the value of moderate exercise in improving the autonomic dysfunction and in inducing a cardiovascular reconditioning. Based on these available evidences from animal and human studies, strengthening and cardiovascular exercises may help maintain function and do not adversely affect disease progression in persons with ALS [6]. However, the current evidence is not sufficiently detailed to recommend a specific exercise prescription for ALS patients. In the present study, it has been designed an exercise program based on both moderate endurance training and isometric muscle contractions (in muscle strength in the mild to moderate range with MRC score $\geq$3). The aim is to verify the clinical efficacy of this exercise protocol, thorough an objective assessment of the changes of muscular strength, the fatigue and the cardiovascular parameters. ALS pts admitted for rehabilitation treatment and enrolled with the inclusion criteria (clinically defined or probable ALS, the El Escorial criteria; mild-moderate disability; no heart and respiratory failures); 11 patients with ALS (7 males and 4 females aged 50 ± 13 years, range 24 ± 75 years) participated in the study; mean duration of the disease was 27 months (range 10 ± 66 months); at the time of the study, the patients had a total ALSFRS-R score from 21 to 41 (mean value, 31.7 ± 6.0). The exercise protocol consists in isometric muscle

contractions, proposed in muscle strength in the mild to moderate range (with MRC score 3 and 4) and in a aerobic training by bicycle ergometry, arm-leg ergometry and/or treadmill with frequency of 4-5 sessions per week using an initial training intensity corresponding to 60–70% of maximum heart rate. Initial exercise duration of 15–20 min is recommended depending on the disability level of the ALS patient. We performed the following evaluations (before/after rehabilitation): ALSFRS-R (revised ALS functional rating scale), IB, Functional Independence Measure (FIM), Fatigue Severity Scale (FSS), strength measurements (MMT by dynamometer); analysis of HR variability and Oxygen Intake (VO2 submax), six minute walking (6MWT) and ten meter walk test (10MWT). The project is a pivotal trial. 4 pts have presented a drop-out for rapid disease deterioration; the other 7 pts have concluded the study. Decrease in fatigue as measured by a fatigue measurement tools at two months; the Fatigue Severity Scale and the change of the VO2submax have presented a reduction. Increase of muscle strength, as measured by the MMT dynamometry; the pts have presented an increase of MMT dynamometry scores; in 5 pts during the 6MWT the distance has presented an increase. In conclusion, the effects of therapeutic exercise in ALS patients are controversial and not well understood. The aim of this project has been to understand the clinical outcomes of moderate load endurance and isometric resistance exercise protocol. If confirmed, these findings may represent a translational step to establish exercise prescriptions and to improve the clinical practice in ALS.

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