News Release

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ATS Press Room: 504-670-6926 (May 15 to 20)

Press conference time: May 16, 11:15 a.m. in the ATS Press Room (E-1)

Mini-symposium: 1:30- 3:45 p.m. May 17
Location: CC-Room 386-387 (Third Level), Morial Convention Center

Neuromuscular Electrical Stimulation Reduces Muscle Atrophy in COPD

ATS 2010, NEW ORLEANS— Neuromuscular electrical stimulation (NMES) may reduce muscle atrophy in patients with severe chronic obstructive pulmonary disease (COPD), according to Canadian researchers.

The results will be reported at the ATS 2010 International Conference in New Orleans.

NMES is the application of electrical stimulation to a group of muscles through electrodes placed on the skin. It is primarily used by physical therapists to help restore function to injured muscles. Isabelle Vivodtzev, Ph.D. and colleagues wanted to test whether NMES had the potential to address muscle wasting in COPD patients.

Muscle wasting is common in patients with severe COPD, and effective treatment has yet to be developed. The impact of muscle wasting and poor limb muscle endurance on survival and

functional status in COPD has been clearly established. General physical reconditioning is currently the best treatment to improve limb muscle function in this disease, but there is a need to develop alternative tools to treat limb muscle dysfunction. Up to a third of patients with COPD undertaking exercise training do not show the expected gain in functional status or muscle function.

“Because it has little impact on ventilatory requirements and dyspnea, NMES appears as a promising alternative to general physical reconditioning in advanced COPD and its feasibility has been confirmed in this population,” said Dr. Vivodtzev, a postdoctoral student at l’Institut Universitaire de Cardiologie et de Pneumologie du Québec.

To investigate whether NMES could effectively reduce muscle wasting in COPD patients, the researchers recruited 20 patients with severe COPD (FEV1<50% expected) to be randomly assigned to receive home-based NMES or sham treatment (wherein electrical stimulation was applied, but at a very low frequency so as to induce tremor sensation without true muscle contraction) for 30 minutes, five days a week over six weeks, in a double-blind study.

Training with NMES led to significant reduction in the level of Atrogin-1 protein which is involved in muscle protein degradation, and, maintenance of the level of $p70^{S6K}$ protein, which is involved in protein synthesis in the NMES-trained patients as compared with sham group. Furthermore, changes correlated with changes in intensity of stimulation during NMES training suggesting that changes at cellular level were modulated via a dose-response manner.

“NMES improved quadriceps and calf muscle mass. Improvements in quadriceps muscle mass were positively correlated with changes in the level of proteins involved in muscle signalling pathway,” said Dr. Vivodtzev. “These results suggested that NMES training would increase the anabolism to catabolism ratio in muscle proteins of COPD patients and prevent muscle-wasting.”

“Our result also confirmed that NMES could improve walking distance and muscle strength in COPD patients. Similarly to what observed at cellular level, the patients who were able to increase the intensity of stimulation during the whole training program also improved muscle strength and walking distance to a greater extent than the patients who kept the same intensity of training from the beginning to the end of training,” said Dr. Vivodtzev.

Dr. Vivotzev expected that muscle electrostimulation would improve walking and exercise capacity in COPD, as the effect had been previously described in the literature in COPD patients. However she and her colleagues were surprised to discover that certain patients were better tolerant to high intensity of stimulation than others, with better improvements in muscle strength and walking distance after NMES.

"If borne out by further research, our study would set the physiological foundations upon which future clinical utilizations of muscle electrostimulation could be based," concluded Dr. Vivodtzev. "In the long term, we wish to contribute to therapeutic development in the area of limb muscle dysfunction in COPD as this should lead to better functional status, quality of life and survival."

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"Molecular Mechanisms of Muscle Hypertrophy After Neuromuscular Electrical Stimulation in Patients with Severe COPD" (Session B97, Monday, May 17, 1:30-3:45p.m., CC-Room 386-387 (Third Level), Morial Convention Center; Abstract 2104)

**Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Molecular mechanisms of muscle hypertrophy after neuromuscular electrical stimulation in patients with severe COPD

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Rationale: The mechanisms by which neuromuscular electrical stimulation training (NMES) may improve muscle mass are poorly understood. We investigated the effect of NMES of lower limbs on muscle cellular signaling pathways in severe COPD.

Methods: 20 patients (FEV_1 < 50 % pred., 6MWD < 400 m) were randomly assigned to NMES (n = 12) or SHAM (n = 8) training in a double-blind controlled study. Training was performed at home (30 min, 5 days/wk) for 6 weeks. Quadriceps and calf muscle cross sectional area (CSA) and the protein level of AKT, atrogin-1, the phosphophrylated form of AKT (pAKT), $p70^{S6K}$, glycogen synthase kinase-3β (GSK-3β), eukaryotic translation initiation factor 4E binding protein-1 (4E-BP1), and the mRNA expression of atrogin-1, muscle ring finger (MuRF) protein 1 and forkhead box class O (FoxO)-1 in quadriceps were evaluated.

Results: After training, quadriceps and calf CSA improved with NMES as compared to SHAM training (+6 ± 2 vs. -1 ± 1 % and +6 ± 2 vs. -2 ± 2 %, respectively, $p < 0.05$). The atrogin-1 protein level (catabolism) was reduced after NMES training ($p = 0.01$). The $p70^{S6K}$ protein level was maintained after NMES as compared with a reduction after SHAM training ($p = 0.03$). The changes in quadriceps and calf CSA correlated positively those of pAKT to total AKT ratio ($r = 0.69$, $p = 0.02$) and of $p70^{S6K}$ ($r = 0.75$, $p = 0.003$). The changes in pAKT correlated with the NMES training intensity ($r = 0.80$, $p = 0.009$).

Conclusions: Improvement in muscle mass after NMES in patients with COPD was associated with a more favourable anabolic/catabolic balance.