Can Diaphragm pacing delay non invasive ventilation in amyotrophic lateral sclerosis? A randomized controlled study

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ALS is characterized by a progressive degeneration of motor neurons, leading to progressive weakness of muscles, including respiratory muscles, the diaphragm. Although specific therapy is lacking, correct respiratory therapy improves quality of life and increases survival. Substituting the failing respiratory muscles by non invasive mechanical ventilatory assistance (NIV) is the current standard of care.

Benefits of electrical stimulation in neuromuscular diseases

It is clearly established that the trophic effect of the muscular fiber is influenced by its motor neuron activity. The application of this knowledge led in the 90s to the electrical stimulation, first, of muscular fibers and then of muscular groups in animals with muscular dystrophy. These animal trials, with patterns of electrical stimulation at low frequencies, showed a positive effect on the trophicity of muscle fibers. This was subsequently confirmed in patients with Duchenne de Boulogne muscular dystrophy (DMD). Unfortunately, due to the extent of the muscular dystrophy, coupled with the impossibility of stimulating all the muscles simultaneously, the clinical interest was never verified and this potential treatment was abandoned.

Recently however, electrical stimulation proved to be of clinical interest in fascioscapulohumeral muscular dystrophy where, in contrast with DMD, the muscular dystrophy is selective (the facial and shoulder girdle muscles, eventually spreading to pelvic, abdominal, humeral, and anterior foreleg muscles). Electrical stimulation is at times being used again in DMD to maintain certain muscles groups, particularly the quadriceps.

On the other hand, diaphragmatic stimulation has been successful for years, due to the localized muscular group requiring stimulation. Electrical stimulation of the diaphragm is called: « Intradiaphragmatic phrenic stimulation ».

Intradiaphragmatic phrenic nerve stimulation is a new treatment and has been the object of a preliminary international proof-of-concept multicenter trial. This trial suggests that the intradiaphragmatic phrenic nerve stimulation slows down the rate of decline of the diaphragm. Intradiaphragmatic phrenic stimulation consists of 4 Intramuscular electrodes implanted laparoscopically at the motor point of the diaphragm, recruiting the phrenic nerves and allowing the diaphragm to contract. There are 2 validated indications for this technique: High level spinal cord trauma and acquired or congenital Central Hypoventilation (www.has.fr, Haute Autorité de Santé/SED/SEAP/SEESP/2009).

This technique now has the CE mark which also mentions ALS. In this particular indication, the goal is not to produce ventilation but to slow down the deterioration of the diaphragmatic function due to the disease through a trophic type action.The clinical trials described earlier showing the benefits of neurostimulation at low frequencies even on dystrophic locomotor muscles. The recently demonstrated benefits of the training of the respiratory muscle enabling it to maintain its function, first of all in DMD and more recently in ALS.

Moreover, intradiaphragmatic phrenic stimulation, at low frequencies and small amplitudes, proved not to be noxious in the ALS animal model (muted SOD Rats on the chromosome). In the same study, a negative effect with high stimulation parameters was also verified. This is also known with high level of physical exercise in humans with this disease. Unfortunately, these ALS animal models do not allow for a long enough reeducation phase of the diaphragm to really assess the clinical benefit, especially as the rats do not survive once the locomotor muscles are deteriorating and consequently they need to be sacrificed.

In the light of these results and after a pilot study, an international multicenter pivotal clinical trial was recently completed using intradiaphragmatic phrenic stimulation in ALS patients (NCT00420719). The preliminary data shows a slowdown in the degradation speed of the respiratory function in response to the phrenic stimulation (see below), and a better sleep quality (ALSJournal 2011, Gonzalez-Bermejo et coll). It is strongly suggested that the intradiaphragmatic phrenic stimulation could slow down the respiratory decline sufficiently to delay significantly the need for NIV.

In summary our new hypothesis is that phrenic stimulation induces diaphragm conditioning and can delay the need for mechanical ventilation in ALS patients. We will study, during 24 months, 2 groups of 37 patients at the beginning of the respiratory dysfunction, using an intradiaphragmatic phrenic nerve stimulation in one group and a sham stimulation in the other group. Although, all the patients will be implanted, thus, at the end of the study, all the patients will receive effective stimulation.

RespiSTIM-ALS - Can Diaphragm pacing delay non invasive ventilation in amyotrophic lateral sclerosis? A randomized controlled study

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ALS is is characterized by a progressive degeneration of upper and lower motor neurons, leading to progressive weakness of bulbar, limb, abdominal but also respiratory muscles (the **diaphragm** and the **accessory respiratory muscles**). Although specific therapy is lacking, correct respiratory therapy improves quality of life and increases survival. Substituting the failing respiratory muscles by non invasive mechanical ventilatory assistance (NIV) is now a current standard of care.

Intradiaphragmatic phrenic nerve stimulation (the motor nerve of the diaphragm), has been the object of a preliminary proof-of-concept multicenter trial (ALSJournal 2012, Gonzalez-Bermejo and al.) in ALS. The aim of our new study is to test the hypothesis that phrenic stimulation induced diaphragm conditioning can delay the need for mechanical ventilation in ALS patients.

74 Patients presenting with very early signs of respiratory impairment (Vital capacity between 80 and 60%), but with a preserved electromyographic response of the diaphragm to phrenic nerve stimulation, will be randomized in 2 groups. All the patients will be implanted with a phrenic stimulator, and then randomized between actual diaphragm conditioning or sham stimulation during 2 years on maximum. Respiratory function will be followed up on a trimonthly basis. NIV (+active stimulation for both groups), will be initiated according to currently recommended criteria of hypoventilation or at the end of the 2 years if no hypoventilation appears. The main outcome of the study will be the number of months between the randomisation and the introduction of NIV. Currently available data, showing that diaphragm pacing can increase the number of patients without NIV at 2 years from 2,5% to 15% of the patients, requires the enrollment of 37 patients in each group. Secondary end-points will include i.Survival ii. Effects on sleep iii. Quality of life and daily activities but also, for the first time in a disease, a bank of diaphragm biopsies (Myobank-AFM, Paris)

This is a french multicenter study (inclusion in the 19 ALS centers of France) with fundings from the french government (*Programmes hospitalier de recherche clinique*), *Fondation Latran* and *Association de Recherche sur la SLA*. The maximal duration of the study will be 4 years (2 years of inclusion, 2 years of follow up). Patients inclusions started in 2012.

Figure 1: Implant of one electrode in the right diaphragm.