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Muscle training with repetitive magnetic stimulation of the quadriceps in severe COPD patients☆

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Summary
Background: Previous studies have used electrical neuromuscular stimulation as a physical training method in patients with severe COPD. We introduce the use of the more tolerable magnetic stimulation for the same purpose, investigating the effectiveness of an eight-week protocol.
Methods: Eighteen patients with severe COPD were randomly assigned to a magnetic stimulation training protocol, $n = 10$, $FEV_1 = 30\%$ (SD: 7) or to parallel clinical monitoring, control group, $n = 8$, $FEV_1 = 35\%$ (SD: 8). During eight weeks, patients were stimulated for 15 min on each quadriceps femoris, three times per week. Quadriceps muscle strength and endurance measurements, quality-of-life questionnaires (SF36, SGRQ) and a six-minute walking test were all carried out before and after the training period in the stimulated and control subjects.
Results: All patients completed the training with increasing intensity of stimulation, displaying a significant improvement in voluntary quadriceps strength (17.5% of the baseline value) and exercise capacity, with a mean increase of 23 m in the six-minute walking test. The questionnaire scores showed greater increases in quality-of-life scores in the trained subjects compared to the controls, particularly in the physical function areas: mean increments in SF36 in ''physical function'': +26, ''role limitations due to physical problems'': +40 and ''vitality'': +17.5, while +13, −4 and +1, respectively in controls. Saint George's ''Activity'' score improved by 19.6 points, for 11.5 in controls.

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Conclusions: In COPD patients who are limited due to dyspnoea, magnetic neuromuscular stimulation of the quadriceps constitutes a feasible training method for the lower limbs, with positive effects on the muscle function, effort capacity and perception areas.
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Introduction

Atrophy and dysfunction of the striated skeletal musculature lead to reduced exercise capacity, impaired quality of life and increased mortality in patients with chronic obstructive pulmonary disease (COPD).[1,2] In a high proportion of COPD patients, in spite of their extremely abnormal respiratory function, it may be the sensation of muscular fatigue, rather than the dyspnoea, that is first to limit exercise capacity.[3,4] A great deal of evidence exists as to the serious dysfunction of the quadriceps muscle in COPD, with loss of type I fibres and reduced oxidative capacity, phenomena that have been linked to impaired quality of life, reduced exercise capacity and increased use of healthcare resources.[5,6] The quadriceps, as the subject of standardized, routine muscle function measurements such as maximal voluntary contraction or supramaximal magnetic twitch, has become an indicator of the condition of the musculature of the lower limbs.[7,8]

High-intensity exercise of the lower limbs, encompassed within what is known as ''respiratory rehabilitation,'' is accepted as a treatment option with grade A evidence.[9,10] However, in severe COPD, training, although beneficial, is not easily feasible and fully accomplishable, due to the fact that an effort-overload is required from the patient. In patients who are beyond this ''window of opportunity for rehabilitation,'' interval training, Heliox or oxygen supply and other strategies have been trialled, in an attempt to make the most of their cardio-respiratory reserves.[11]

Another alternative that has been raised is neuromuscular stimulation of the lower extremities, with positive results having been obtained using electrical stimulation, especially in more severe or muscularly-compromised COPD patients,[12–16] while simultaneously inducing minimal cardio-respiratory overload.[17] Although effective for increasing muscle strength, electrical stimulation may also produce some painful sensations, which, in selected subjects, may prevent the stimulus from being applied to a sufficient degree in order to achieve maximal activation.[18,19] Magnetic stimulation bypasses this limitation by producing the stimulus at a deep level, thus avoiding the skin sensation; for this reason it is currently replacing electrical stimulation in diagnostic use.[7] In recent years equipment has become more complex, now including the option of repetitive stimulation, which is necessary for more complex measurements such as muscular fatigue[20] or to act on the muscle as a form of sustained stimulation training. Previous experience in our group included the evaluation of a Medtronic Magpro device with a refrigerated circular MCF125 coil,[21] where the contraction effect measured after its application to the muscle bulk, was comparable to the response to full femoral nerve activation by standard supramaximal quadriceps twitch.[8] In a selected group of patients we also could contribute data on change in fibre types and redox balance after repetitive stimulation.[22] After establishing its suitability for a training protocol, we decided to apply it to stable, COPD outpatients to investigate the hypothesis of its feasibility as a means for respiratory rehabilitation (RR), testing effectivity by direct outcomes of muscle strength and endurance, and by secondary rehabilitation aimed variables as are exercise capacity and quality of life.

Methods

Study type

Randomized controlled clinical trial with the aim of evaluating an eight-week protocol of repetitive magnetic stimulation (rMS) of the quadriceps muscle in COPD patients. The outcomes to be assessed were parameters relating to quadriceps muscle function, effort capacity (six-minute walk distance, 6MWD) and quality of life.

Patients

Eighteen severe COPD patients, with $FEV_1 < 50\%$ (GOLD stages III–IV) and habitual dyspnoea of at least grade II according to the MRC scale[23] were recruited on an outpatient basis from hospital-dependent outpatient clinics. Exclusion criteria were any changes in treatment during the four months preceding the trial, and the presence of heart pacemakers. Comorbidity was taken into account on an individual basis, especially with regard to diseases of the locomotive or cardiovascular systems or neurological disease, as well as treatments that might interfere with implementation of the protocol or with the evaluation of functional outcomes. No participants in previous rehabilitation programs were accepted.

All patients were Caucasian, male and were exclusively on inhaled medication (long-acting beta2-agonists, anticholinergics, and low-dose inhaled corticosteroids). Using a table of randomized numbers, patients were sorted into two groups: one rMS-treatment ($n = 10$) and one control ($n = 8$) group.

Data for both groups ($n = 18$) are shown in Table 1 and demonstrate severe chronic obstruction to the airflow (mean FEV_1: 33.3% (SD: 8.5%) of the predicted value). The majority of patients were not hypo-nourished according to the BMI, which was 26.9 kg/m^2 (SD: 4.4) in the stimulation group and 28.3 kg/m^2 (SD: 3.9) in the control group, a difference not reaching clinical significance. Only two patients in the rMS group were below 21 kg/m^2.

Both groups demonstrated slightly reduced values for muscle strength,[24] both for the MVC-Q, which was 32.3 kg (SD: 14.4) in the rMS group compared to 38.1 kg (SD: 10.5) in the control group, and for the TwQ, at 7.79 kg (SD: 2.79) in the rMS group and 8.6 kg (SD: 2) in the control group (n.s.).

Table 1 Characteristics of the trained and control subjects, both at the beginning and at the end of the protocol.

	rMS $n = 10$	Final	Control $n = 8$	Final	Inter-group p at baseline
Age (years)	61 (6)		62 (8)		0.79
FEV_1 (% pred.)	30 (7)	31 (7)	35 (8)	35 (9)	0.1
FEV_1/FVC (%)	32 (8)	31 (9)	37 (8)	37 (10)	0.43
BMI (kg/m^2)	25.3 (3.8)	25.3 (4.2)	28.33 (4)	27.9 (4)	0.08
FFMI (kg/m^2)	18 (3.3)	17.9 (3.7)	19.5 (2.3)	19.3 (2.7)	0.3
MVC-Q (kg)	32 (14)	38 (18)*	38.12(10.5)	44 (13)	0.4
MVC-Q/weight	0.455 (0.2)	0.529 (0.2)*	0.53 (0.2)	0.605 (0.2)	0.4
TwQ (kg)	7.8 (2.8)	8.8 (2.3)	8.6 (2)	9.8 (2.2)	0.5
Endurance time	331 (317)	489 (356)	456 (217)	506 (215)	0.4
6MWT (m)	397 (138)	420 (144)*	420.6 (80)	417.5 (65)	0.7
6MWT (pred.)	75.3%	79.7%*	85.2%	84.5%	0.2

Data given as ''mean (standard deviation)''. No significant differences found between rMS and control groups, as shown in the last column. * indicates $p < 0.05$ between initial and final measurements.
Abbreviations: BMI, body-mass index; FFMI, fat-free mass index; MVC-Q, maximal voluntary contraction of the quadriceps; TwQ, quadriceps twitch strength.
Predicted values for 6MWT according to Enright.[32]

The distance covered in 6 min was 397 m (SD: 138), 75.2% of the predicted value[25] in the rMS group compared to 420 m (SD: 80), 87.7% of the predicted value in the controls. The p values resulting from the inter-group comparison are displayed in Table 1.

Study design and procedures

A diagram of the study design is provided in Fig. 1. All 18 patients received information about the investigation, the procedures that would be carried out and their risks, and provided written consent, as approved by the Cruces Hospital Ethics and Clinical Trials Committee. Regarding outcomes evaluations, all patients were subjected to identical assessments and functional procedures.

Evaluation for inclusion included performing clinical anamnesis and physical exam, evaluation of chest X-ray and general blood exam and biochemistry, including creatine kinase (CK) and lactic dehydrogenase (LD). The following measurements were taken both during the week before the start of stimulation treatment and in the five days following its completion:

Pulmonary function tests

Health-related quality of life, using the SF36[26] and the Saint George Respiratory Questionnaire (SGRQ),[27] both self-administered.

Body composition: fat-free mass (FFM) was determined using the bioelectric impedance method[28] (Bodystat-500; Bodystat Ltd, Douglas, UK) and expressed as a fat-free mass

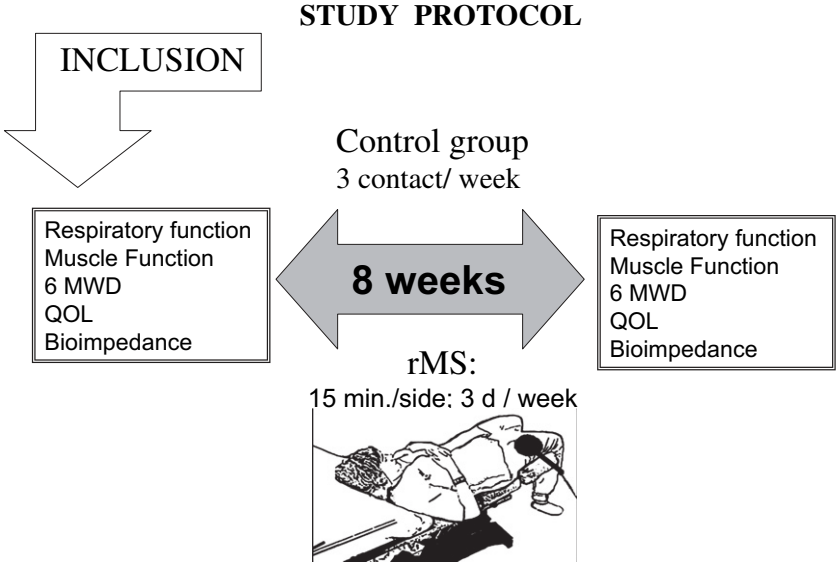

Figure 1 Diagram representing the repetitive magnetic neuromuscular stimulation protocol, including a demonstration of the placement of the stimulation coil on the upper third of the thigh.

index (FFMI), which is the result of FFM/(height)^2, height expressed in meters.[29]

Peripheral muscle function: unpotentiated quadriceps twitch (TwQ) was measured on both limbs with a Magstim 200 electromagnet, after a prior 20-minute rest period and observing the protocol and patient position according to the technique described by Polkey.[8] The Biopac dynamometer (TSD 121C) signal was amplified via a Biopac system (Biopac System, La Jolla CA, USA), sent to a PC and processed using previously calibrated digital polygraphy AcqKnowledge® software.

Maximal voluntary contraction of the quadriceps (MVC-Q) was measured using five maximum isometric contraction efforts (knee-extension attempts) using the same couch and patient position as for the TwQ.

QTlim or endurance test: performed according to the Coronell method,[30] the endurance parameter being the maximum sustainable time for leg extensions of the dominant leg while bearing 10% of the weight of the MVC-Q. The test started after at least 15 min rest, in an identical posture to MVC-Q testing. The rotational adjustment and the angle of the knee were similar in all patients. The contraction pattern was set to 12 contractions per minute with a load of 10% of the MVC-Q, allowing two seconds' contraction and three seconds' relaxation; the rhythm was regulated by an audio-digital signal (Joggler Plus 4.8.1; Leepoware, San José, CA, USA). End of testing was determined according to Coronell's criteria.[30]

Six-minute walking test (6MWT): This test was always carried out over the same 30 m stretch, according to the described procedure.[31] A minimum of three measurements was carried out in the initial assessment and two during post-protocol evaluation.

rMS training protocol: training sessions were started between one and two weeks after the initial assessment. Patients in the rMs group were subjected to repetitive magnetic stimulation in sessions of 15 min on each thigh, three days per week, for a period of eight weeks. The assessment was repeated in the five days following the end of this period.

Stimulation: repetitive magnetic stimulation training of the quadriceps, rMS, was carried out using a MEDTRONIC Magpro MCF125 electromagnet with a refrigerated circular coil of 60 mm radius, applied at the point between the upper third and the lower two-thirds of the vastus lateralis, the optimum location for eliciting a contraction response, as determined by our volunteer validation study.[21] Patients were in a sitting or recumbent position with the knee flexed at 90°and the ankle fixed by a strap as seen in Fig. 1.

The intensity and frequency of stimulation were adjusted according to the patient's tolerance and the performance of the equipment. Stimulation followed a cyclical pattern of two seconds *ON*, with contraction elicited by a burst of twitches, and four seconds *OFF*, repeated over a period of 15 min on each thigh. With the coil being cooled in advance to 5 °C, it was possible to maintain an initial intensity of 40% of the equipment's maximum stimulation capacity (2 T) at 15 Hz (stimulus per second), ending the protocol at an intensity of 70% at 7 Hz. Since preventing patient discomfort was a major concern, the intensity was increased by 2−3% every two sessions, on the condition that the patient had not reported pain caused by the stimulation or unpleasant sensations following the previous session. In these cases patients were examined and blood samples were submitted to determine CK and LD.

Control group: patients received two check-up visits and one telephone call per week (a total of three contacts per week), during which they were actively asked about respiratory symptoms. Physical activity was recommended, but no repetitive magnetic stimulation at any intensity was given.

Additional information is available in a Supplementary file online.

Statistical analysis

The nonparametric Mann−Whitney test was used for comparison between groups, while Wilcoxon's test for paired data was chosen to evaluate the effects of the (training or control) intervention within each group. Comparison of the inter-group differences was achieved by comparing the percentage change per variable. Correlations between variables were analysed using Spearman's nonparametric coefficient. Statistical significance was taken as $p < 0.05$. The 95% confidence interval (CI) was calculated between the differences in measurement, basal condition and following treatment in the different groups.

Results

Tolerance of rMS sessions

It was possible to complete the stimulation sessions satisfactorily in all patients with the intended increases in intensity, reaching the limit of 70%, pre-established as the maximum stimulus based on the availability of coils and refrigeration periods. It was also possible to achieve the minimal increase of 3% every two sessions, with only mild muscle soreness reported occasionally by patients. These symptoms did not persist and no analytical variations in muscular enzymes (CK and LD) were observed in anyone. Patients were compliant with the treatment sessions, fulfilling the schedule, both in rMS and control groups.

Outcomes of the rMS group compared to the control group

Pulmonary function and body composition

No significant changes occurred to these parameters in either group.

Muscle strength parameters

The changes in muscle function, in terms of maximal voluntary manoeuvres, supramaximal twitch and endurance are reflected in Fig. 2. After the eight weeks of the investigation, MVC-Q increased in both groups, by 17.5% (95% confidence interval (CI): 6.7%; 27.6%) in the rMS group ($p = 0.005$) compared to 15.7% (CI: 0%; 30%) in the control group ($p = 0.06$). The TwQ also increased, but in a non-significant manner, by 15.6% (CI: −5%; 29%) compared to 14.3% (CI: −6%; 34%).

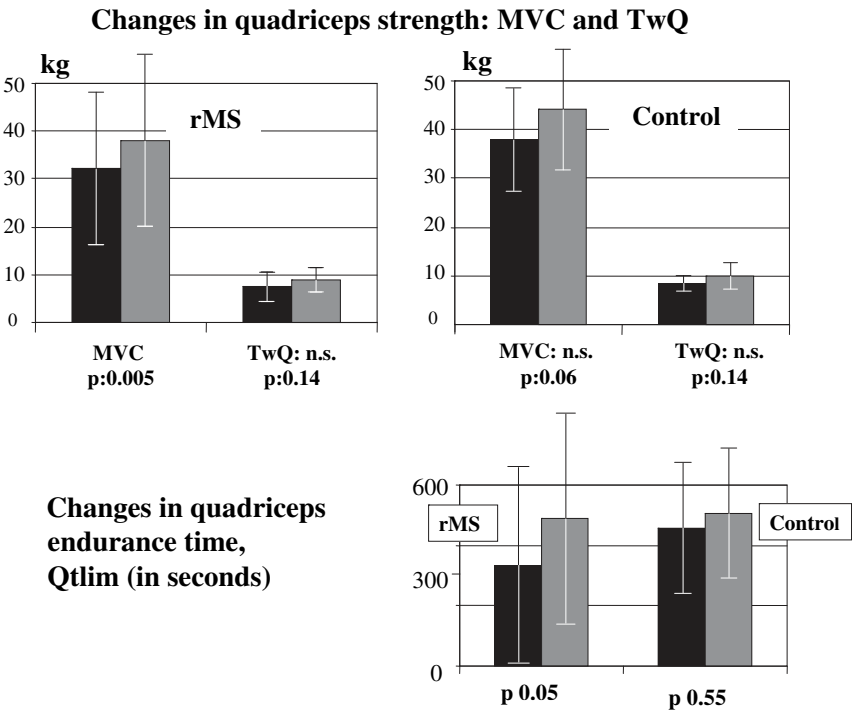

Figure 2 Changes in muscle function: parameter values represented as columns and ±SD bars. Upper section: Changes in maximal voluntary contraction of the quadriceps (MVC-Q) and supramaximal twitch values (TwQ) between the start (black column) and the end (grey column) of the investigation, both for rMS (left panel) and control (right panel) groups. Lower section: changes in quadriceps endurance over time for both groups, showing mean changes between the start (black) and end (grey) of the study period.

Muscle endurance

With regard to muscle endurance, the time that the load was able to be supported in the stimulated group increased by 44% (CI: −1%: 97%), from 331 to 489 seconds ($p = 0.05$), compared to an 11% (CI: −30%: 51%) increase in the control group (from 456 to 506 s; $p = 0.548$), represented in the lower graph of Fig. 2.

Exercise capacity

The changes in the six-minute walking test for both groups are displayed in Fig. 3, which shows that the distance covered changed only in the rMS group, with an increase of 23.4 m (CI: 11; 36), compared to a minimal change of −6 m (CI: −18; 24) in the control group.

Health-related quality of life

The results of both groups for the general SF36 questionnaire and the specific Saint George Respiratory Questionnaire (SGRQ) are reflected in Fig. 4.

At the start of the study no inter-group differences were found in quality of life using either of the questionnaires. As can be observed in Fig. 4, following the rMS training, decreases in score were greater in all areas of the SGRQ and the increases in the SF36 were greater and more significant. While quality of life improved for both groups, the greater differences for the rMS group are worthy of note, and are particularly accentuated in the physical function areas of the SF36 (''physical functioning'' and ''role limitations due to physical problems''). In these two areas the differences for the rMS group were +26 (CI: 10; 36) and +40 (CI: 12; 68) compared to the non-significant changes in the control group. The ''energy/vitality'' area showed a mean 17.5 point increase (CI: 0.5; 35), compared to 3.15 (CI: −5; 11) in the non-trained subjects. In the SGRQ the greatest difference was visible in the ''activity'' area, with a decrease of −19.4 (CI: −4; −35) compared to −15 (CI: −5; −26) in controls. Impact of disease improved after training by −17.5 (CI: −7; −29), but worsened slightly in controls: +5.7 (CI: −7; 17).

Discussion

Study contributions

This is the first study to use a magnetic stimulating device for repetitive neuromuscular stimulation of the quadriceps for the purpose of rehabilitation in COPD patients. It has demonstrated the applicability of the technique and that it causes positive outcomes in areas such as effort capacity and quality of life, which impact on patients' functional capabilities that are important for prognosis.[32]

The design of a protocol for repetitive neuromuscular stimulation of the quadriceps using a magnetic stimulating device was based, on the one hand, on data gathered from assessing the Medtronic equipment on volunteers[21] and, on the other hand, on previous investigations that incorporate electrical stimulation therapy into traditional respiratory rehabilitation programmes.[9,12–16] These protocols were adapted, in duration and intensity, to the technical

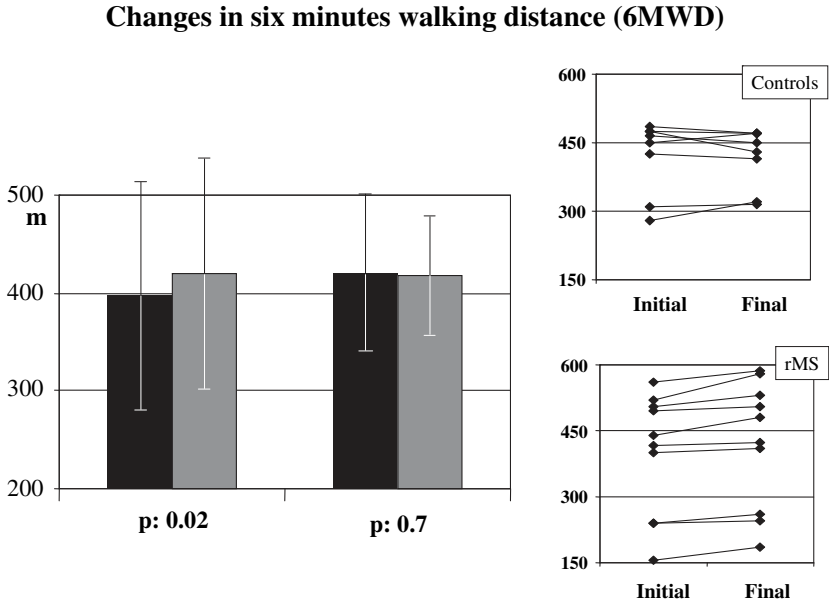

Figure 3 On the left, mean changes for each group on the left for the six-minute walking test, between the start (black) and end (grey) of the protocol, shown as columns and ±SD bars. On the right, initial and final values for the individual patients in both groups.

capacities of our Medtronic stimulation equipment, in order to introduce this innovative method, which is hypothetically at least as effective as electrical stimulation, into the rehabilitation context.[9]

Reasons backing up the technique

Transcutaneous electrical stimulation studies have consistently demonstrated effectiveness in decreasing dyspnoea and increasing muscle strength, effort capacity,[15,16] and maximum O_2 consumption in stable, moderate-to-severe COPD patients.[17] A systematic review of studies by Roig[12] indicates that more severe patients show greater benefits after treatment. Its use during convalescence from acute episodes or critical conditions involving mechanical ventilation and prolonged periods confined to bed has been shown to prevent functional deterioration and to shorten recovery time.[13,14]

Despite various authors[18,19] reporting that there may be limitations to performing muscle training via electrical stimulation in specific subjects, sufficient experience has arisen to indicate that this is a feasible treatment option in COPD and heart-failure patients. We have here considered repetitive magnetic neuromuscular stimulation as another option that could potentially have at least similar tolerability and effects.

The idea arose after testing a Medtronic electromagnet on the thigh, which elicited a contraction response equivalent to 80% of supramaximal femoral twitch, with high reproducibility and a ceiling of response.[21] It seemed consistent with these findings that muscle contractions caused by repeated magnetic stimuli encompassing large, deep muscle-sections should have a training effect, thus opening up new treatment possibilities.

One limitation of stimulating devices, despite the refrigerated coils, is the thermogenic effect of the high-intensity electrical currents running through them. Consequently, the maximum stimulus frequency was adjusted between 15 and 7 Hz, in order to complete the study with increasing stimulus intensity. Despite these frequency adaptations, the visible contraction response increased in parallel with the intensity, probably due to a known facilitation effect.[7]

Proven outcomes

In the stimulated patients, a 5.55 kg increase of voluntary strength in the quadriceps was found, a 17.5% increase in MVC-Q, similar to that which has been observed using electrical stimulation in patients with substantial muscular deterioration,[15] in particular, following critical situations or acute episodes.[13,14] The literature states that strength training seems to provide little benefit when added to exercise-based rehabilitation programmes.[33] This is true when the benefits are evaluated using general exercise parameters, but not in terms of quality of life, to which these methods make significant changes.[33,34]

The stimulated patients in this study showed significant increases in endurance time, with a mean increase of 158 s per patient, much greater than the 48-s increase recorded in the control group. The fact that the differences were greater for endurance than for muscle strength, suggests that this procedure might constitute a type of ''endurance training'' and although magnetic and electrical stimulation concepts might not be interchangeable, the outcome profile for our protocol would seem to be more similar to that of low-frequency than high-frequency electrical stimulation.[35] Previous data on redox status and fibre-type changes support this interpretation, as muscle oxidative

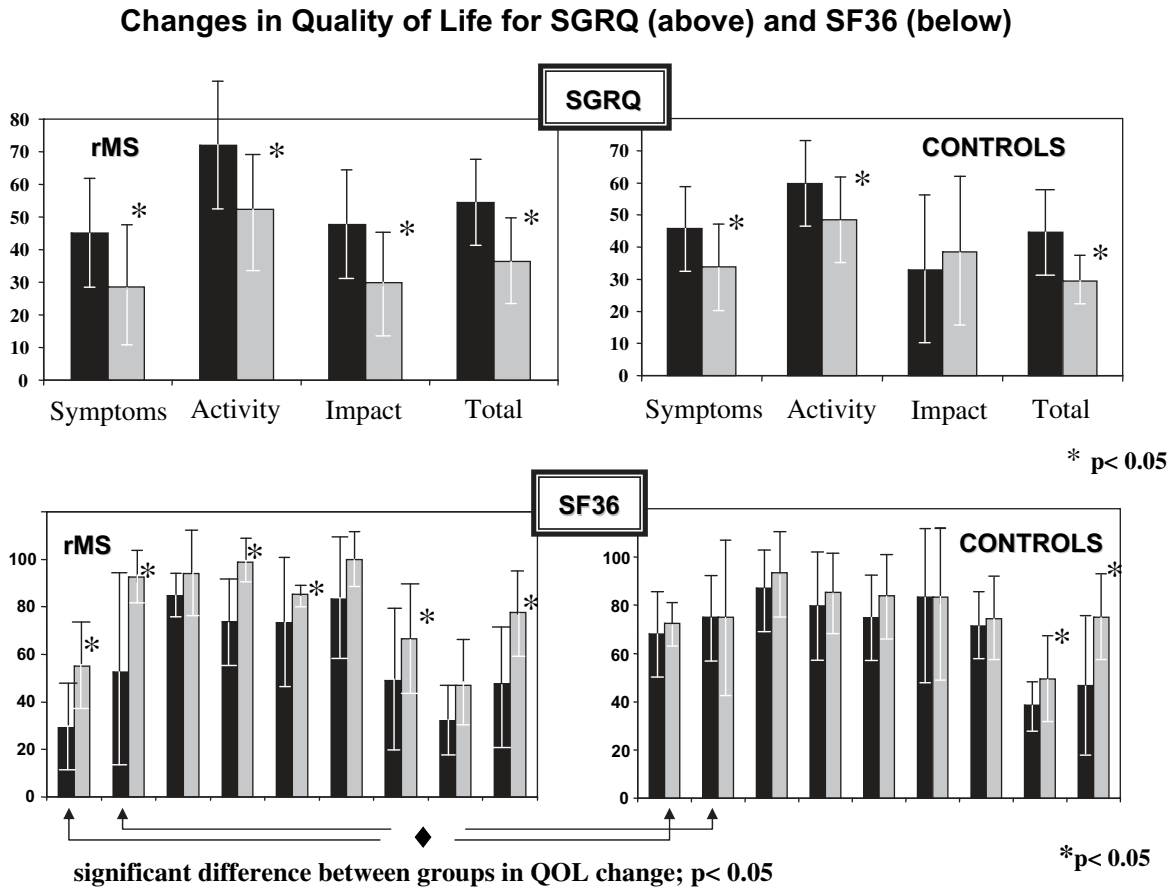

Figure 4 Changes in the quality-of-life tests, for the SGRQ (above) and the SF36 (below), represented as mean scores ±SD. SGRQ: For the rMS group, all four areas (* $p < 0.05$) improved significantly (symptoms, activities, impact and total) and for the control group: symptoms, activity and total, in a smaller degree. SF36: changes in the QOL scores are shown in this order: physical functioning,* role limitations due to physical problems,* bodily pain, social functioning,* mental health,* role limitations due to emotional problems, vitality,* general health perception and changes over time.* In the control group, the only significant differences are general health perception* and changes over time.* (*$p < 0.05$). As stated in the bottom legend, arrows indicate differences in QOL changes between the two groups. (◆: inter-group difference $p < 0.05$).

stress was not enhanced, while the size of slow-twitch fibres increased.[22]

The observed outcome with regard to exercise capacity following eight weeks of training with magnetic stimulation was a mean increase of 23.4 m in the distance walked over six minutes, performed according to standard practice.[31] This increase was seen in almost all patients and does not appear attributable to a learning effect, since it was not observed in the control group. While a ''threshold of clinical significance'' of 54 m has been set in the literature,[36] based on quality-of-life changes for patients, in our opinion it appears promising that an approach other than specific exercise training should display an effect, however small, on exercise capacity. To back up this line of thought, the combined effect of electrical stimulation with exercise training achieved a positive gain of 63 m in the six-minute walking test, compared to the 30 m achieved by the standard rehabilitation treatment,[13] suggesting that muscle stimulation can increase the benefits of respiratory rehabilitation. It has been documented for electrical stimulation that ''weaker'' patients do improve most after muscle stimulation,[12] this being the reason to be concerned by the fact that our rMS group patients showed slightly lower 6MWD and BMI values at baseline, a circumstance that could explain the greater benefit they might have received from any intervention.

Parallel monitoring of both groups leads us to attribute changes in quality-of-life questionnaires in non-rMS patients to a placebo effect, most evident in general health perception and changes over time in the SF36 and in all areas of the SGRQ except in that of ''impact of the disease''. Nevertheless, the magnitude of the changes was greater in the rMS group for all areas of the SGRQ and in the areas of the SF36 related to physical functioning, role limitation due to physical problems, vitality and social functioning. These changes in physical function, both in the sphere of symptoms and of impact of the illness, are those that might be related to the effects of magnetic stimulation. Similarly, with electrical stimulation, other authors have found general improvements in quality of life, particularly related to dyspnoea, not observed in the control patients.[13,15]

Study limitations

Unlike the application of surface electrodes for electrical stimulation, there is a lack of prior experience with magnetic stimulation used outside of the diagnostic sphere. The fundamental interest in trialling this method resides in the improved tolerance hypothesis, but the novelty, complexity and high cost of stimulating devices mean that general experience in handling this equipment is extremely limited, for which reason our initial investigation had to be staged at a rather basic level.[21] After achieving some experience with the technique, we felt confident to apply it to patients in a pilot study such as the present one, in order to document changes in the main areas in which the effectiveness of exercise-based rehabilitation treatment in COPD patients has been reported.[9]

While the feasibility and tolerance of the trialled stimulation protocol have been proven, it has still not been determined which are the optimum intensity, frequency and stimulation duration sequences (depending on the available equipment, including the quantity and sophistication of the coils) and which patients could benefit most from this treatment, whether in combination with traditional rehabilitation, or not.

Conclusions

An rMS programme has demonstrated improvements in muscle function parameters, effort capacity and quality of life in severe COPD patients.

It can be postulated that this stimulation method might be an alternative for patients incapable of engaging in conventional rehabilitation exercise. It is also a well-tolerated, promising option for patients debilitated due to an intercurrent acute disease, bedridden or in intensive care units, in which respiratory rehabilitation is not appropriate or may even have negative effects.

Competing interests

None of the authors has a financial relationship with any commercial entity that has an interest in the subject of this manuscript.

Supplementary data

Supplementary data associated with this article can be found in online version at doi: 10.1016/j.rmed.2009.10.001.

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