

A Simpler and Shorter Neuromuscular Electrical Stimulation Protocol Improves Functional Status and Modulates Inflammatory Profile in Patients with End-Stage Congestive Heart Failure

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Abstract

Background: Neuromuscular electrical stimulation (NMES) using a stimulation wave for 5 days/week over 8 weeks has been used as a treatment option for congestive heart failure (CHF) patients who are unable to tolerate aerobic exercise.

Objective: We assessed the impact of a shorter NMES protocol using a Russian stimulation wave on the functional status, quality of life (QoL) and inflammatory profile of end-stage CHF patients.

Methods: Twenty-eight patients with end-stage CHF (53 ± 11 years) were randomized to the NMES or control group. Treatment was an NMES training program with Russian stimulation wave, applied for 50 minutes to both quadriceps femoral muscles twice weekly over seven weeks. The stimulation intensity was chosen to elicit muscle contractions in the NMES group and current input up to sensory threshold in the control group. Distance in the 6-minute walk test (6MWT) and QoL score by the Minnesota Living with Heart Failure Questionnaire were evaluated before, immediately after and one month after NMES protocol completion. Peripheral leukocytes were obtained to measure the gene expression levels of inflammatory cytokines.

Results: The NMES group showed increases in the 6MWT (324 ± 117 vs. 445 ± 100 m; $p = 0.02$) and QoL score (64 ± 22 vs. 45 ± 17 ; $p < 0.01$) immediately but not 1 month after protocol completion, as well as increased gene expression levels of IL-1 β , IL-6 and IL-8 after protocol completion.

Conclusion: Using a shorter and fewer sessions NMES protocol improved the QoL score and functional class of severe CHF patients, and modulated the gene expression levels of some cytokines. This protocol might be a good alternative for patients with severe CHF and limitations in protocol adherence. (Int J Cardiovasc Sci. 2017;30(6)484-495)

Keywords: Heart Failure; Exercise Tolerance; Electric Stimulation Therapy / adverse effects; Exercise; Rehabilitation; Heart Transplantation.

Introduction

Exercise intolerance is a challenging issue for patients with severe congestive heart failure (CHF)^{1,2}, who commonly exhibit fatigue and dyspnea. Patients with stable CHF should perform aerobic exercise training protocols to decrease muscle weakness caused by lack of physical activity, as well as to improve functional status, exercise capacity and quality of life (QoL).³⁻⁵

However, some patients are unable to perform aerobic exercise training protocols due to exercise intolerance or an unwillingness to participate in such programs.^{2,6} As an alternative to muscular training therapy in patients with CHF or chronic obstructive pulmonary disease (COPD), neuromuscular electrical stimulation (NMES) may be used to improve functional status, exercise capacity, endothelial function and QoL.^{2,3,6-8} NMES has been demonstrated to modulate inflammatory mediators

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in patients with spinal cord lesions⁹ and athletes after a bout of running.¹⁰ However, the effects of NMES on the inflammatory profiles of CHF patients have not been well documented.

Common NMES training protocols involve treatments over 5 to 6 days/week for 6 to 8 weeks. These intensive therapy protocols may preclude some CHF patients from adhering to this treatment modality^{2,3} because, similarly to other exercise training protocols, patients may be unwilling to attend the outpatient clinic daily for treatment.^{2,3,7,8,11} Most studies of NMES-treated CHF patients have employed functional electrical stimulation,^{2,7,13,14} which causes muscle contractions. Another NMES electric waveform modality is the Russian current, which involves the application of a 2500-Hz current at a burst frequency of 50 Hz. This modality effectively produces muscular strength in normal individuals¹⁵⁻¹⁷ and may be more comfortable than other current modalities for patients during NMES sessions.^{15,18,19}

The Russian current has a sine waveform, which has been reported as more comfortable for the patient during the electrical delivery to the muscle. Of note, the Russian current has an average frequency with a deeper stimulus effect and may be more tolerable by the patient.²⁰⁻²²

The unique characteristics of the Russian current might increase patient adherence to the NMES protocol. Therefore, the aim of this work was assess the effectiveness, compared to the literature, of a shorter NMES protocol consisting of twice-weekly training for 7 weeks using a Russian current, in terms of the functional status, QoL score, and inflammatory profile in patients with CHF.

Methods

Patient selection

Institutional Review Board approval was obtained for the study, and all patients provided written informed consent to participate. To be included in the study, patients must be on the awaiting heart transplant list, NYHA functional class III or IV, receiving optimal oral pharmacological treatment, and have stable CHF symptoms in the last 3 months. Exclusion criteria were neurologic or orthopedic disease that could limit the patient's ability to accomplish the 6-minute walk test (6MWT). This study is registered at www.clinicaltrials.gov under the number NCT02313714.

Protocol for NMES

This study was carried out at an outpatient clinic of a university hospital with a room temperature maintained between 22 and 24 °C. NMES was applied by 2 adhesive electrodes on the skin over the upper lateral aspect of the quadriceps muscle, 5 cm below the inguinal fold and 3 cm above the upper patella border of both lower extremities (Figure 1).

In the NMES group, the stimulator (Neurodyn 2000, Ibramed, Amparo, SP, Brazil) was configured to deliver a direct electrical current with a 2500-Hz sinusoidal current at a burst frequency of 50 Hz (Russian current) for 3 seconds, followed by 9 seconds of rest. The intensity of stimulation was adjusted to achieve visible contraction. The stimulus intensity is adjusted according to patient tolerance. However, in order to be sure that muscle fiber contraction is occurring, the visual evaluation of at least one visible contraction is used. From this levels of contraction and patient's comfort we adjusted higher levels of intensity and the highest level of intensity is adjusted according to patient's tolerance.²³

During electrical stimulation sessions, the legs were positioned in a light knee flexion position in both groups. In the control group, the same setup was used with 2 adhesive electrodes in the identical position as above, and the stimulator was configured to deliver a direct electrical current with the same specifications (Russian current). The intensity of stimulation was set low, to achieve a sensation of stimulus but with no visual muscular contraction.

Patients in both groups were evaluated weekly. The protocol was applied for 50 minutes twice a week, Wednesdays and Fridays, for 7 weeks.

Distance in the 6MWT

The 6MWT was performed in a 30-meter-long indoor hallway of the university hospital. Patients were trained and oriented to walk as fast as possible with encouragement. Only after the patient was considered trained was the walked distance recorded. All 6MWT sessions were carried out by the same observer (MCBS) in accordance with the American Thoracic Society (ATS) instructions.²⁴ To ensure the patient's safety and consistency in 6MWT application, the modified Borg scale was applied before, during and after the 6MWT to evaluate the patient's self-perception of dyspnea and fatigue. The 6MWT was performed at 3 time points:



Figure 1 – Placement of adhesive electrodes over the quadriceps femoral muscle. A single set of double adhesives was used as a simple way of applying neuromuscular electrical stimulation.

immediately before the first NMES session, 1 day after the last NMES session and 1 month after termination of the NMES protocol.

QoL by the Minnesota Living with Heart Failure Questionnaire (LHFQ)

A Portuguese language version of the LHFQ²⁵ was utilized to assess the QoL score 1 day before starting the NMES protocol, 1 day after completing the 7-week NMES protocol, and 1 month after protocol termination. The LHFQ is a questionnaire tool consisting of 21 questions, including physical and emotional variables. This questionnaire provides one score, with a scale from 0 to 105. Higher scores are associated with a worse QoL status. The LHFQ is a very frequently used score to assess QoL and is a reliable way to measure changes over time in the QoL of patients with CHF.¹³⁻²⁶

Gene expression by peripheral leukocytes

Blood samples were drawn 1 day before NMES protocol initiation and 1 day after the last NMES session

(7 weeks). Peripheral leukocytes were isolated from blood by centrifugation at 1100 rpm for 10 minutes in a refrigerated centrifuge (4 °C). Total RNA was isolated from the cellular pellet by using TRIzol® LS reagent (Ambion, Life Technologies, USA). Total RNA was quantified by using the 260/280 nm absorbance ratio data. The High-Capacity cDNA Reverse Transcription kit (Applied Biosystems, Carlsbad, CA, USA) with 1 µg of total RNA was used for reverse transcription reactions. To assess different levels of gene expression, quantitative real-time PCR was performed with the Taqman Fast Advanced Master mix (Applied Biosystems) and commercially available Taqman primers for IL-1α, IL-8, TNF, IL-10 and IL-6 (Applied Biosystems). The *GADPH* gene was used as an internal control.

Outcomes

The primary outcome of the study was the change in 6MWT after completion of the 7-week NMES protocol. The secondary outcome was the QoL score after completion of the 7-week NMES protocol.

Statistical analyses

All continuous data with Gaussian distribution are reported as means \pm standard deviations (SDs). All continuous data with no Gaussian distribution are reported as median and range. All variables were assessed for normality distribution using Shapiro-Wilk test.

Discrete variables are described as the frequency of the corresponding population. Analyses of the 6MWT and QoL score were performed by two-way analysis of variance and the Tukey post hoc test for detecting which time points were different. Correlations between the 6MWT and QoL score were calculated by linear regression analysis. Analyses of demographics were performed using t test or Mann-Whitney where was appropriated. Analyses of baseline characteristics and medication were performed using chi-square test.

A simple random sampling was used to allocate patients to the 2 groups. An online tool was employed for the group draw (www.graphpad.com). The sample size was based on previous studies^{12,13,26} and on the availability of inpatient/outpatient hospital facility. A P value smaller than 0.05 was considered statically significant.

All calculations were conducted and figures were constructed with GraphPad Prism software (version 6 for Mac OS X, GraphPad Software, La Jolla, CA, USA).

Results

Overall results

Of the 36 patients with severe CHF who were on the awaiting heart transplant list and initially assessed for the study, 8 patients refused to participate. The remaining 28 patients with end-stage CHF were randomly divided into 2 groups. Patients in the NMES group ($n = 18$) underwent treatment with the 7-week NMES protocol using the Russian current. Patients in the control group ($n = 10$) were tested with a similar protocol using an ineffective electric current. One month after termination of the treatment protocol, 9 patients in the NMES group and 5 patients in the control group were assessed. Figure 2 shows the flowchart of patient enrollment for the entire cohort. All patients were medicated for CHF, and the medication was not changed during the study period. The groups did not show differences regarding the distribution of

sex, age, demographics, medication, body mass index or functional class (Table 1).

Safety of NMES application

During the 7-week protocol, no NMES-related complications were observed in either group. One month after protocol termination, 1 patient in the NMES group had experienced cerebral vascular stroke, 2 patients in the NMES group had died due to CHF complications, and 2 patients in the NMES group and 1 patient in the control group had undergone heart transplant (Figure 2).

Improvement of the 6MWT with the 7-week NMES treatment

Compared to before treatment, 6MWT was increased immediately after the 7-week treatment in the NMES group (324 ± 117 vs. 445 ± 100 m; $p = 0.02$) but returned to baseline values by 1 month after protocol termination (324 ± 117 vs. 317 ± 194 ; $p = 0.89$). The control group showed no differences in 6MWT values between before and after treatment (Table 2).

Improvement of the QoL scores with the 7-week NMES treatment

Compared to pretreatment values, the NMES group showed improvement in QoL scores after completion of the 7-week NMES protocol (64 ± 22 vs. 45 ± 17 ; $p < 0.01$), whereas the control group showed no differences. However, the QoL scores in the NMES group had returned to the baseline values by 1 month after protocol termination (64 ± 22 vs. 51 ± 20 ; $p = 0.07$) (Table 2).

Association of QoL score with pretreatment 6MWT

Before commencement of the NMES protocol, the 6MWT was not associated with the QoL score in either group (Figures 3A and B). In the control group, no correlation was found between the pretreatment 6MWT and the posttreatment QoL score (Figure 3C). However, the pretreatment 6MWT was inversely correlated with the QoL score obtained immediately after completion of the treatment (Figure 3D). The pretreatment 6MWT was directly correlated with the 6MWT obtained immediately after treatment in both groups (Figure 3E and F).

Table 1 – Baseline characteristics, demographics and medication

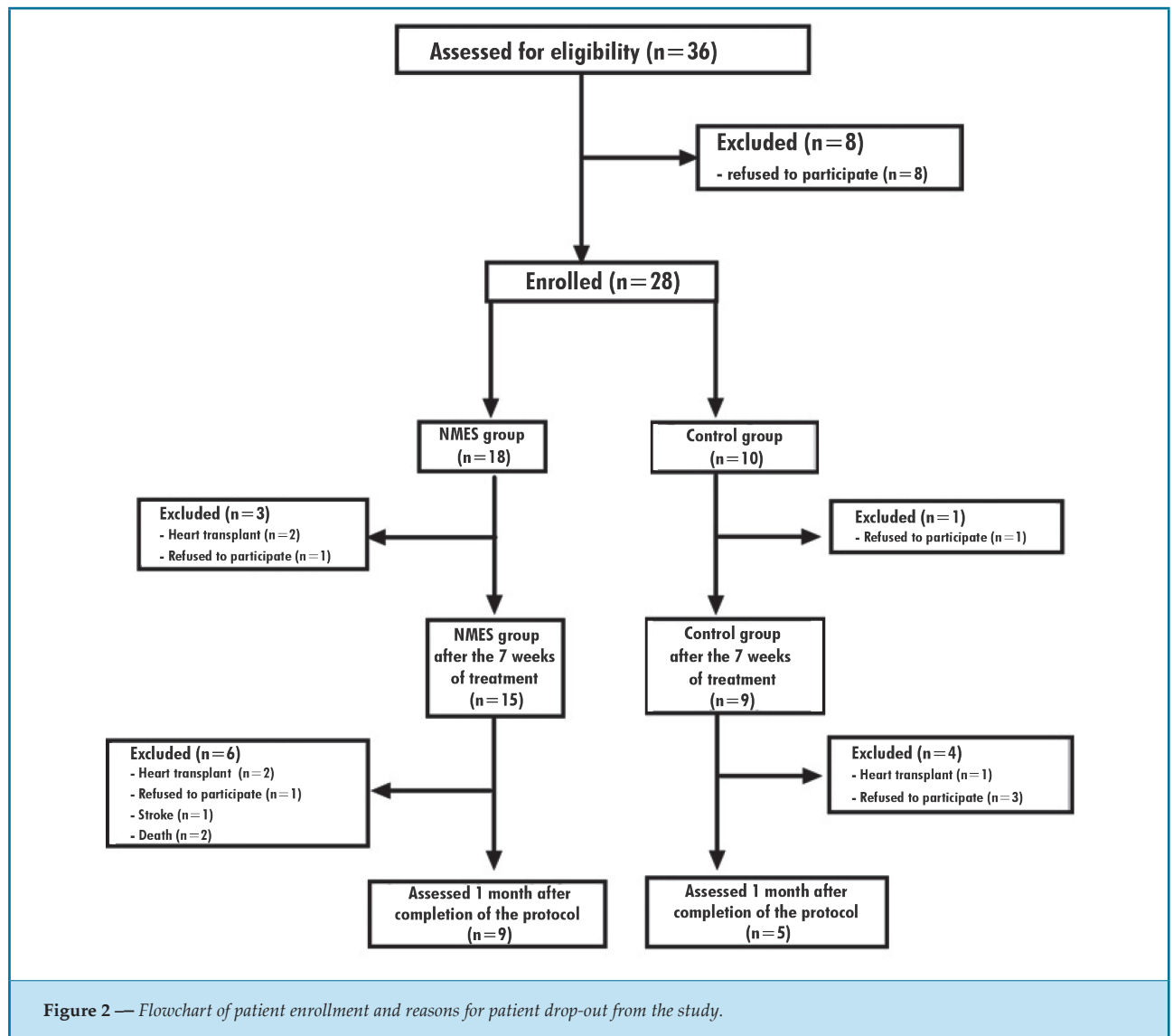
Characteristic	NMES group (N = 18)	Control group (N = 10)	p-Value
Gender			
Male	15 (83)	9 (90)	0.93**
Female	3 (17)	1 (10)	
Age, years	54 ± 10	50 ± 12	0.39*
Height, cm	163 ± 28	172 ± 6	< 0.01*
Weight, kg	86 ± 22	80 ± 13	0.13*
BMI, kg/m ²	27 ± 5	26 ± 5	0.85*
Ejection fraction, %	30 ± 10	34 ± 10	0.90*
CHF etiology			
Idiopathic	6 (33)	4 (40)	0.51**
Ischemic	8 (44)	2 (20)	
Valvar	2 (11)	2 (20)	
Chagas's disease	1 (6)	2 (20)	
Viral	1 (6)	0 (0)	
Functional class			
III	13 (72)	9 (90)	0.54**
IV	5 (28)	1 (10)	
Medications			
Diuretics	18 (100)	10 (100)	0.71**
Espironolactone	15 (83)	9 (90)	0.86**
Digoxin	11 (61)	5 (50)	0.68**
Beta-blocker	16 (89)	10(100)	0.79**
Antiarrhythmic	0 (0)	1 (10)	0.71**
Antiplatelet	11 (61)	60 (60)	0.89**
Statin	9 (50)	2 (20)	0.33**
Ca ²⁺ channel blockers	3 (17)	0 (0)	0.52**
Nitrates	4 (22)	2 (20)	0.86
ACE inhibitors	13 (72)	9 (90)	0.22

Data are reported as n (%) or mean ± standard deviation. BMI: body mass index; diuretics include furosemide and bumetamide; ACE: angiotensin-converting enzyme. (*) P value using t test. (**) P value using Chi-square test.

Modulation of gene expression with the 7-week NMES treatment

Compared to pretreatment values in the control group, the gene expression levels of IL-1 β , IL-6, and IL-8

were increased immediately after protocol completion in the NMES group (Figure 4A–C). No modulation of IL-10 or TNF gene expression was observed in either group (data not shown).

**Table 2 – Hemodynamic values, functional capacity and quality of life**

Parameter	Pretreatment		Immediately posttreatment		1 month posttreatment	
	NMES (n = 18)	Control (n = 10)	NMES (n = 15)	Control (n = 9)	NMES (n = 9)	Control (n = 5)
Resting HR, bpm	74 ± 14	74 ± 9	68 ± 16	72 ± 7	73 ± 11	73 ± 8
Resting SBP, mmHg	101 ± 11	110 ± 10	115 ± 66	103 ± 16	101 ± 8	108 ± 13
Resting DBP, mmHg	66 ± 8	70 ± 8	67 ± 7	67 ± 8	69 ± 6	68 ± 8
LHFQ	64 ± 22	51 ± 25	45 ± 17 [†]	52 ± 25	51 ± 20	48 ± 24
6MWT, m	324 ± 117	393 ± 151	445 ± 100 [†]	353 ± 159	317 ± 194	366 ± 92

HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; 6MWT: distance in the 6-minute walk test; LHFQ: score on the Minnesota Living with Heart Failure Questionnaire; [†] Before treatment vs. immediately after treatment $p < 0.05$ (within NMES group).

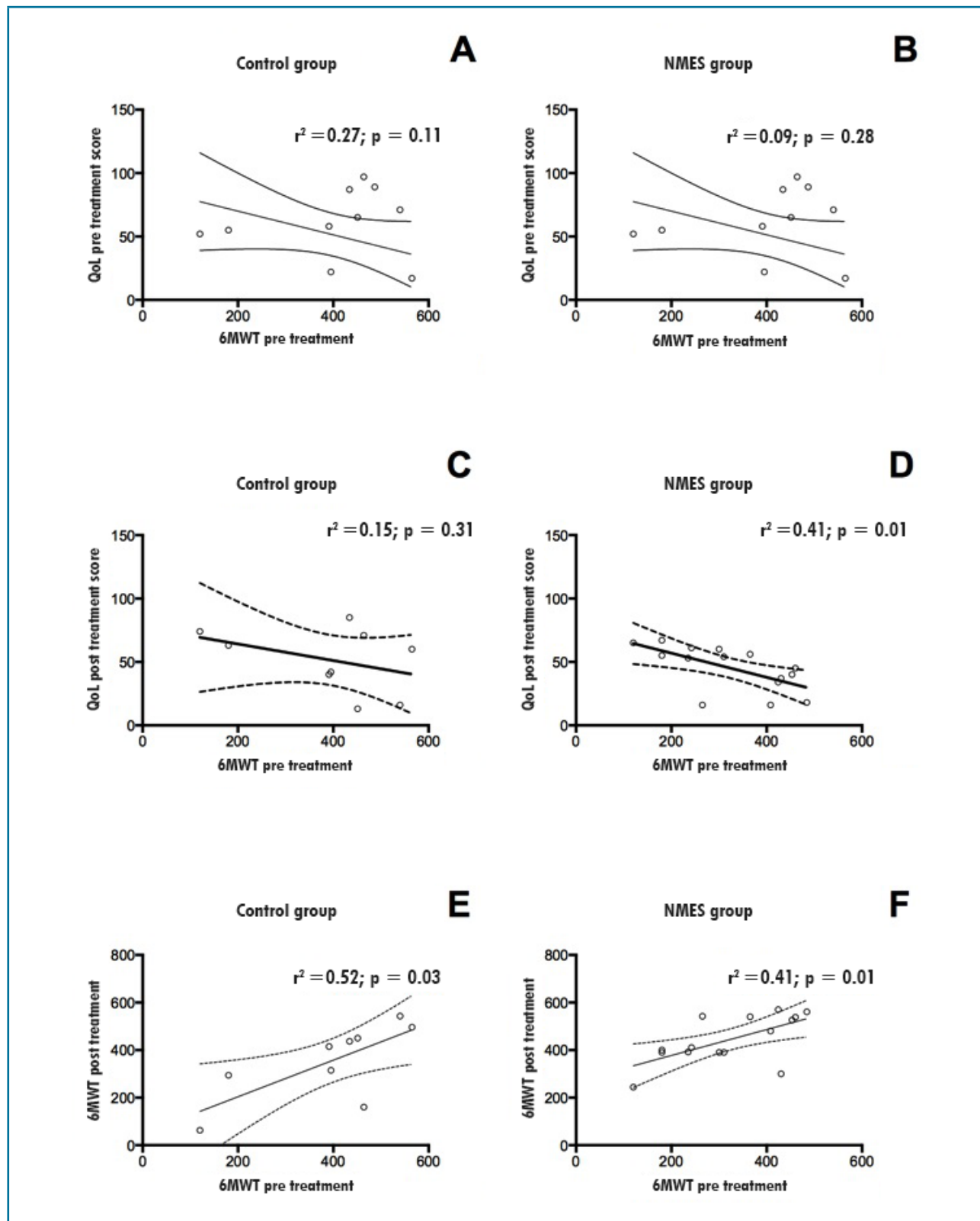
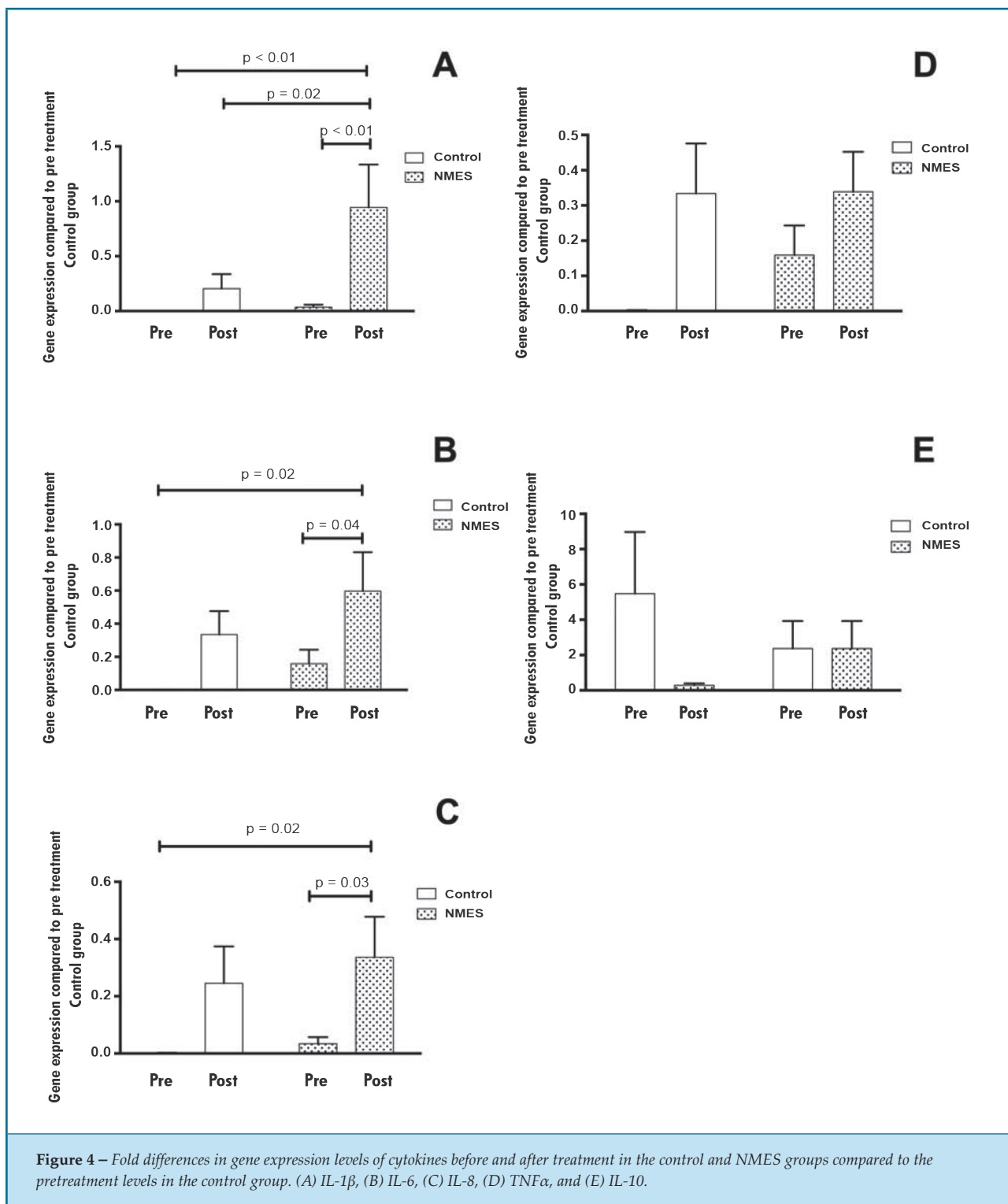


Figure 3 – Correlations among the pre- and/or post-treatment distance walked in the 6-minute walk test (6MWT) and quality of life (QoL) in the control group (A, C, E) and NMES group (B, D, F).



Discussion

We found that the application of a shorter NMES protocol, exclusively to the quadriceps femoral muscles improved the functional capacity and QoL

scores and modulated the inflammatory profiles of patients with severe CHF. This less-intense NMES protocol provided similar beneficial effects to those obtained with longer and more vigorous NMES protocols.^{2,3,6,7,27} Thus, this modified protocol could be

an alternative solution for greater patient adherence to a rehabilitation program.

NMES using a Russian current is a well-known and safe modality for treating patients and improving their comfort during NMES sessions.^{15,18,19} NMES has beneficial effects for functional capacity in patients with different diseases and conditions, including CHF, severe COPD, stroke, and osteoarthritis, as well as patients in intensive care units.^{3,28} The 6MWT was used to determine functional capacity in this study and has been commonly utilized for this purpose in previous reports.^{26,29} The 6MWT has a good correlation with peak oxygen consumption (VO₂), and changes in the 6MWT can be used to predict mortality.^{6,27}

The novelty of the present work lies in the less-frequent application of NMES through a simple pair of adhesive electrodes, which are placed on the skin over the quadriceps femoral muscle in each limb. All previous studies have used protocols with FES (Functional Electrical Stimulation) current ranging from 5 to 7 days per week.

All previous studies have enrolled patients with CHF of functional classes II and III, whereas the present study enrolled patients with functional classes III and IV on the awaiting heart transplant list.

Of note, we did not find in the literature studies that had evaluated a shorter protocol and using this specific type of current (Russian current) in a rehabilitation programs with patients in this specific clinical profile. Additionally, we did not find data reporting a longer training protocol that evaluated the functional capacity and quality of life following the discontinuation of electrical stimulus. We believe that a shorter protocol may improve patient adherence to the rehabilitation program, which is a day by day problem on those patients.

Previous studies of NMES protocols generally have utilized 8 adhesive electrodes in each limb.^{2,3} Using a more intense NMES protocol design of 8 adhesive electrodes applied for 30 minutes/day, 5 days/week for 6 weeks, Parissis et al.² reported improvements in QoL, functional status, emotional status and endothelial function in patients with stable systolic CHF (NYHA class II or III).² We demonstrated similar QoL and functional status results in sicker patients (NYHA functional class III or IV), using an less-demanding protocol with 1 pair of adhesive electrodes applied for 50 minutes/day, 2 days/week for 7 weeks. Banerjee et al.³⁰ observed increases in the 6MWT and VO₂ after 8 weeks of

NMES training in patients with CHF and low left-ventricular ejection fraction. They utilized a more complex stimulation apparatus, composed of adhesive electrodes applied at multiple muscles (quadriceps, hamstrings, calves and gluteal muscles) in each limb.³⁰ Other authors have demonstrated similar results to the present manuscript regarding the functional capacity after training with more intense NMES protocols, such as 5 days/week for 30 to 60 minutes/day over 5 to 8 weeks.^{13,31,32}

Several papers have demonstrated an improvement of QoL after NMES, as assessed by different questionnaires, such as the Beck Depression Inventory, Zung Self-Rating Depression Scale¹² and Kansas City Cardiomyopathy Questionnaire.¹² The LHFQ, which was used in the present study,²⁶ is increasingly being applied for the assessment of QoL in patients with CHF.^{8,13,33} The QoL score was improved immediately after completion of the NMES protocol, consistent with several reports in the literature using different NMES protocols.^{2,7,8}

The QoL score has consistently demonstrated to improve with NMES and low-intensity aerobic exercise programs; however, the durability of these effects has not been frequently reported. We found that the QoL scores had deteriorated to near-baseline levels by 1 month after protocol completion. Patients who walked longer distances during the 6MWT before NMES treatment were more likely to have better QoL scores immediately after completing the NMES protocol in the NMES group. However, the pretreatment 6MWT and QoL values were not correlated with each other in either group. These findings support the use of the 6MWT as a useful tool for assessing QoL after NMES treatment in this subset of patients. Several studies have reported improvements of the 6MWT and QoL score after NMES, but, to our knowledge, a relationship between both has not been reported.^{7,33}

Some reports have demonstrated favorable effects of either aerobic and isometric exercises on inflammatory modulation in, for example, healthy individuals³⁴ and patients with paraplegia or rheumatic disease.³⁵ In CHF patients, data regarding the inflammatory profile after any physical exercise protocol have been inconsistent.³⁶ Overall, it seems that physical activity may decrease serum TNF levels, with little to no effect on serum IL-6 and IL-10 levels.³⁹ Additionally, very few papers have evaluated the effect of NMES on the inflammatory profile. In their study of severe COPD patients, Vivodtzev et al.³⁷ described no changes in the serum levels of TNF,

IL-6, C-reactive protein (CRP) or insulin-like growth factor-1 (IGF-1) after 6 weeks of NMES application to the quadriceps and calf muscles. A single report studying CHF patients in functional class II or III assessed the endothelial function and immune response after NMES therapy for 5 days/week over 6 weeks.²⁶ This study observed decreased levels of TNF, soluble intercellular adhesion molecule (sICAM), and soluble vascular cell adhesion molecule (sVCAM-1) between before and after NMES treatment. Interestingly, no differences in the serum levels of IL-6 were observed in the control or NMES group.

The present work is the first to describe gene expression from peripheral leukocytes, which may resemble the inflammatory profile, before and after NMES treatment. Using a shorter NMES protocol, we observed increased gene expression levels of IL-6, IL-1 β and IL-8. Measuring gene expression by peripheral leukocytes is a useful and reliable method for assessing diseases, such as asthma and seasonal diseases.^{38,39} The observed increased gene expression of these cytokines may represent a response to the local stress caused by NMES, which is similar to the stress caused by intense physical exercise.^{40,41} The chronic exercise may decrease the inflammatory response. However, in the present protocol is hard to tease out the chronic stimulation (the entirely protocol) from the acute phase. It is possible to say that the NMES modulates the inflammatory response, but we can not say whether or not increase or decrease it.

No previous study has followed patients for 1 month after completion of the NMES protocol. Surprisingly, we observed that the beneficial effects observed immediately after NMES termination were not permanent. The functional capacity and QoL scores returned to baseline values by 1 month after NMES protocol termination. These findings encourage the use of other strategies when implementing the shorter NMES protocol. Nevertheless, the most important aspect of our shorter protocol is that it could facilitate access to a different rehabilitation program. The protocol is composed of only a few sessions per week and does not cause fatigue or dyspnea comparable to conventional therapy (i.e. aerobic exercise training). These factors might stimulate treatment adherence and produce equivalent results to more intense NMES protocols or aerobic exercise training protocols.^{12,30,32,42-45}

Although the present findings are motivating, they must be considered in the context of the study

limitations. As a prospective study, we kept adherence to the randomization draw before the study initiated. The randomization generated blocks of studied groups and not a single patient selection. This trial included a relatively small number of patients with a different group size, although most studies on the same subject have enrolled similar numbers.^{6,12,13,26,31,32}

We observed a more frequent negative events in the treatment group compared to the control group after termination of the training period. It is not possible to exclude whether is related to the termination of the protocol or random. It is important to highlight that there are no data in the literature evaluating patients after termination of the training period and this is the first work that tries to show this information. However, it seems important to keep special attention on the patients after terminating the electrical stimulation protocol period. Moreover, some patients discontinued treatment before protocol completion due to cardiac transplant or death.

Conclusion

Using a shorter and simpler NMES protocol improved the QoL score and functional status in patients with end-stage CHF. The clinical improvement of these patients was accompanied by a increase in gene expression of some cytokines in peripheral leukocytes. This modified treatment might be an interesting alternative for physical rehabilitation in these very sick patients, and may provide similar results compared to longer protocols described in the literature.

Author contributions

Conception and design of the research: Sacilotto MCB, Lavagnoli CFR, Petrucci Junior O. Acquisition of data: Sacilotto MCB, Lavagnoli CFR, Vilarinho KAS, Oliveira ESB, Carvalho DD, Oliveira PPM, Coelho-Filho OR, Petrucci Junior O. Analysis and interpretation of the data: Sacilotto MCB, Vilarinho KAS, Carvalho DD, Petrucci Junior O. Statistical analysis: Sacilotto MCB, Petrucci Junior O. Obtaining financing: Petrucci Junior O. Writing of the manuscript: Sacilotto MCB, Carvalho DD, Petrucci Junior O. Critical revision of the manuscript for intellectual content: Sacilotto MCB, Silveira-Filho LM, Vilarinho KAS, Carvalho DD, Oliveira PPM, Petrucci Junior O.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by FAPESP.

Study Association

This article is part of the thesis of Doctoral submitted by Maria Carolina Basso Sacilotto, from Universidade Estadual de Campinas – Unicamp.

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