ORIGINAL PAPER

EFFECTS OF NEUROMUSCULAR ELECTRICAL STIMULATION IN PATIENTS WITH ACUTE HEART FAILURE – RESULTS OF A SINGLE-CENTER RANDOMIZED TRIAL

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Abstract. *Objective: We evaluated the effects of neuromuscular electrical stimulation (NMES) therapy on functional capacity and oxidative stress in patients hospitalized for acute heart failure (AHF). Design: We included 30 consecutive patients admitted for AHF with a left ventricular ejection fraction ≤ 50% who were randomized into two groups: NMES therapy added on conventional rehabilitation (CR) (n = 15, 67.2 ±13.35 years) and CR alone (n = 15, 63.26 ± 10.29 years). NMES therapy was performed at the level of the quadriceps muscle bilaterally, daily, for 60 minutes with a frequency of 10 Hz. Results: The mean duration of NMES therapy was 6.93 ± 2.54 days. Functional capacity assessed by the 6 minute walk test was significantly improved in the group with NMES therapy (p=0.036). The oxidized LDL value showed a decreasing trend compared to the admission value in the group with NMES therapy, but without statistical significance. Conclusion: This paper shows that for patients with AHF, NMES therapy used for a short term and initiated early during the hospitalization period improves exercise tolerance, suggesting the importance and possible necessity of including it as standard cardiac recovery therapy. NMES did not influence the plasmatic value of oxidized LDL.*

Keywords: *cardiac rehabilitation, acute heart failure, neuromuscular electrical stimulation.*

1. INTRODUCTION

Physical effort in heart failure (HF) patients is the main component of cardiac recovery programs. It improves quality of life and functional capacity [1, 2] and has a beneficial effect on the changes in the skeletal muscles as well as on the neuro-hormonal and inflammatory status of patients with HF [3-5]. However, clinical trials excluded recently hospitalized HF patients.

In addition, physical based recovery therapy cannot be used in all patients with HF, especially those with a recent acute decompensation, severe symptoms, old age, and multiple associated comorbidities. In this case, neuromuscular electrostimulation (NMES) therapy may be a safe and effective alternative [6, 7].

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Previous studies have shown that NMES therapy applied to patients with chronic HF improves muscle strength, exercise capacity, quality of life, reduces re-hospitalization rate and depressive symptoms [8-11], including in elderly patients. Oxidative stress has many effects on myocardial structure and function and it is associated with myocardial dysfunction, cardiac remodeling, disease severity and poor prognosis [12-22]. The difficulty in determining reactive oxygen species (ROS) activity in vivo, the presence of confounding comorbidities, and the disappointing results of large clinical trials using antioxidant therapy are unresolved problems indicating that the relationship between ROS and HF is complex.

Plasma levels of oxidized LDL are considered to be a prognostic indicator of mortality in subjects with HF [23] and are associated with a lower left ventricular ejection fraction (LVEF) [24]. Recently, a study performed on HF patients with preserved LVEF showed that exercise training with a duration of 4 weeks is associated with a decrease in the level of plasma oxidized LDL [25].

Most studies evaluating NMES therapy enrolled stable, chronic HF patients with low LVEF and the procedure was performed across several weeks or months. There is little data on the use of NMES therapy in patients hospitalized for AHF, for a short duration, equal to the period spent in the hospital. The purpose of this randomized study was to evaluate the impact of NMES therapy applied during hospitalization on the functional capacity and oxidative stress in patients with AHF compared to standard rehabilitation alone.

2. MATERIALS AND METHODS

2.1. TRIAL DESIGN

It was conducted a prospective (1:1) randomized study to investigate the effects of NMES on top of conventional rehabilitation versus conventional rehabilitation alone on a hospitalized population with AHF. We tracked the impact of NMES on oxidative stress, functional capacity and laboratory prognostic parameters of HF such as atrial natriuretic peptides.

After the patients with AHF were stabilized they were included in the trial with the consent of the attending physician and were randomized by a blinded investigator to control group or NMES therapy. Medications were prescribed according to patients' needs. At the time of enrollment, patients were clinically evaluated and their associated comorbidities and drug therapy were noted. Electrocardiogram (ECG), echocardiography, 6-minute walk test (6MWT) were performed and laboratory samples were collected including oxidized LDL, NT- proBNP, CK, uric acid, lipid profile and PCR. At the time of discharge, all patients underwent a 6MWT and laboratory samples such as oxidized LDL and NT-proBNP were collected again. During the hospitalization period we monitored any adverse events and tolerance to NMES therapy.

This study was performed in accordance with the Declaration of Helsinki and the study protocol was reviewed and approved by the hospital's Ethics Committee (49/2018). At the time of inclusion in the study, patients signed an informed consent form in two copies, one remaining with the patient. This trial is registered at www.ClinicalTrials.gov (unique identifier NCT04310072).

2.2. STUDY POPULATION

30 patients with HF and a LVEF below 50% (echocardiography) were included, admitted consecutively to the cardiology clinic of "Sfântul Pantelimon" Hospital, Bucharest for AHF. The enrollment period was between September 10 and November 20, 2019.

Exclusion criteria were: age under 18 years, acute coronary syndrome in the last month or during index hospitalization, recent myocardial revascularization (in the last 6 weeks), severe ischemic lesions at the level of the lower limbs, life-threatening arrhythmias, uncontrolled blood pressure, high-grade atrioventricular block, acute myocarditis, acute pericarditis, obstructive hypertrophic cardiomyopathy, acute systemic disease, deep vein thrombosis, severe uncorrected primary valvular disease, psychiatric disorders or marked cognitive impairment, active neoplastic disorders except basal or squamous cell carcinoma, other conditions that in the opinion of the investigator do not allow the participation to the study and patient's refusal.

2.3. RANDOMIZATION PROCEDURE AND BLINDING

After the patients were evaluated for inclusion in the study and after signing the informed consent form, they were randomized using the website www.randomization and allocation secrecy was kept by numbered, sealed, opaque envelopes. Considering our intervention protocol, it was not possible to blind the patients and/or the investigator who performed the electrostimulation. However, the other investigators who conducted the 6MWT and performed the randomization and analysis were blinded.

2.4. 6-MINUTE WALK TEST

The 6MWT was performed according to the guidelines of the American Thoracic Surgery Association [26]. The first 6MWT was performed after the attending physician considered it appropriate due to the clinical stabilization of the patients. The second 6MWT was performed at the time of discharge from the hospital. The 6MWT was performed on a corridor 50 meters long. Patients were instructed to walk down the aisle from one end to the other as many times as possible during the given time. The test was performed under the supervision of a blinded investigator and patients were encouraged every minute in a standardized way. At the end of the 6 minutes, the distance covered by the patient was measured.

2.5. BLOOD MEASUREMENTS

The oxidized LDL was determined by ELISA method after a preliminary fasting period of about 6 hours. Blood samples were obtained to measure the plasma NT-proBNP, C reactive protein (CRP), creatinine, sodium, potassium, TGO, TGP, troponin I, urea and hemoglobin levels.

2.6. STUDY INTERVENTIONS

The control group consisted of patients who performed daily active upper and lower limbs exercise in bed and in a stand position (3x10 repetitions, "somewhat hard" on the Borg scale). For patients who underwent NMES therapy, four electrodes (two 50/100 mm and two 50/50 mm, Compex Performance) were placed on the skin above the quadriceps muscle approximately 5 cm below the inguinal fold and 3 cm above the upper patella border.

The electrical stimulation protocol consisted of electrical current at frequency of 10 Hz, 20 seconds stimulation time (time on) and 20 seconds resting time (time off) with variable intensity (until visible muscular contraction) for one hour per day until discharge (Compex). The NMES group also performed the conventional rehabilitation program as described above.

2.7. DEFINITIONS

AHF was defined as a rapid onset or worsening of symptoms and/or signs of HF, a medical condition that requires urgent evaluation and treatment, typically leading to urgent hospital admission [27]. The patients were included in the trial after clinical stabilization, defined as: not requiring non-invasive ventilation, inotrope or vasopressor drugs, no physical signs and symptoms suggestive of worsening cardiac function and the ability to walk on a level surface without fatigue.

2.8. STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistics 20 (Statistical Package for Social Sciences, IBM, Armonk, New York, USA) and MedCalc (MedCalc Statistical Software, Ostend, Belgium). Numeric and categorical parameters were used. Bartlett's test for homogeneity was used to determine if variances between compared variables are equal. Homogeneous numerical variables were expressed as means ± standard deviation and comparisons were made employing the ANOVA parametric test. Inhomogeneous numerical variables were expressed as minimum and maximum values and compared using the Mann-Whitney Wilcoxon two-sample test.

Categorical parameters were expressed as percentages, and associations were assessed with the Chi squared corrected test and expressed as odds ratios (OR) with 95% confidence intervals (95%CI). Multivariate logistic regression models, using the Enter method, were utilized to identify independent predictors of outcome. All P-values were two-sided, and values less than 0.05 were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. RESULTS

In this study, 31 patients were included: 15 in the control group and 15 in the NMES group, 1 patient was lost after randomization due to early discharge for personal reasons; the mean age of the patients were 65.19 ± 11.68 years, 70.97% being male. The clinical

characteristics of the patients are shown in Table 1 and CONSORT flow diagram is represented in Fig. 1. There were no significant initial differences between the groups in terms of age, sex, LVEF, natriuretic peptides, oxidized LDL, serum creatinine and cardiovascular risk factors except for dyslipidemia which was more common in the group with NMES therapy. There were no differences in optimal home-based drug therapy between the two groups except for neprilysin inhibitors, therapy found exclusively in the group with NMES therapy.

The mean duration of NMES therapy was 6.93 ± 2.54 days and the average length of hospitalization was 8.97 ± 4.53 days, with no significant differences between groups (p = 0.24). There were no adverse events in the NMES group, including muscle pain and skin changes related to the application of electrodes except for an episode of QTc interval prolongation in a patient with a cardiac pacemaker without arrhythmic events, subsequently attributed to serum hypopotassemia (considered in this context unrelated to the NMES procedure).

Table 1. Characteristics of studied patients.

	All (n=30)	**NMES (n=15)**	**Control (n=15)**	**p value**
General Characteristics				
Age (years)	65.19±11.68	67.20±13.35	63.26±10.29	0.37
Sex (male), n	22 (70.97%)	9 (60%)	12(80%)	0.23
Diabetes mellitus, n	12 (38.71%)	8 (53.3%)	4 (26.6%)	0.13
Hypertension, n	26 (83.87%)	13 (86.6%)	13 (86.6%)	1
Dyslipidemia, n	21 (67.74%)	13 (86.6%)	7 (46.6%)	**0.02**
Obesity, n	16 (51.61%)	7 (46.6%)	9 (60%)	0.46
Ever Smoker, n	20 (64.52%)	10 (66.6%)	9 (60%)	0.71
Peripheral artery disease, n	7 (22.58%)	1 (6.6%)	6 (40%)	**0.02**
COPD, n	8 (25.81%)	5 (33.3%)	3 (20%)	0.41
Stroke, n	5 (16.13%)	1 (6.66%)	4 (26.6%)	0.14
Pacemaker, n	6 (6.45%)	2 (13.3%)	0	N.A
CRT, n	1 (3.23%)	1 (6.6%)	0	N.A
Ischemic heart disease, n	17 (54.84%)	8 (53.3%)	6 (53.3%)	1
Systolic BP (mmHg)	121.22±17.08	125.46±15.77	119.06±16.81	0.29
Diastolic BP (mmHg)	71.22±13.83	73.40±15.30	70.46±11.74	0.56
HR (bpm)	78.03±22.72	80.13±17.17	75.80±28.30	0.61
Medications, n				
Beta-blockers	23 (74.19%)	12 (80%)	10 (66.6%)	0.41
ACE inhibitors/ARB	13 (41.94%)	7 (46.6%)	6 (40%)	0.71
Diuretics	21 (67.74%)	10 (66.6%)	10 (66.6%)	1
MRA	20 (64.52%)	9 (60%)	10 (66.6%)	0.71
ARNi	2 (6.45%)	2 (13.3%)	0	N.A
Echocardiography				
LVEF (%)	31.29±10.04	34.20±11.32	29.46±7.50	0.18
TDE (msec)	137.45±46.16	159.13±46.88	112.23±30.88	**0.004**
RVSP (mmHg)	36.4±16.98	37.26±18.03	35.53±16.45	0.78
Laboratory measurements				
Creatinine (mg/dl)	1.21±0.47	1.24±0.52	1.12±0.36	0.44
NT-proBNP (pg/ml)	5057 (362–35000)	5084 (362–35000)	4567 (1200–8597)	0.72
Ox LDL (ng/ml)	45 (15 – 403)	48 (20 – 403)	42 (15 – 292)	0.74
Troponin I (ng/ml)	0.2 (0.2 – 1.69)	0.2 (0.2 – 0.67)	0.2 (0.2 – 1.69)	0.43

COPD - chronic obstructive pulmonary disease, ACE – angiotensin converting enzyme, ARB - angiotensin receptor blockers, CRT – cardiac resynchronization therapy, BP – blood pressure, HR – heart rate, TDE – deceleration time of E wave, RVSP – right ventricular systolic pressure, MRA – mineralocorticoid receptor antagonist, ARNi – angiotensin receptor/neprilysin inhibitor

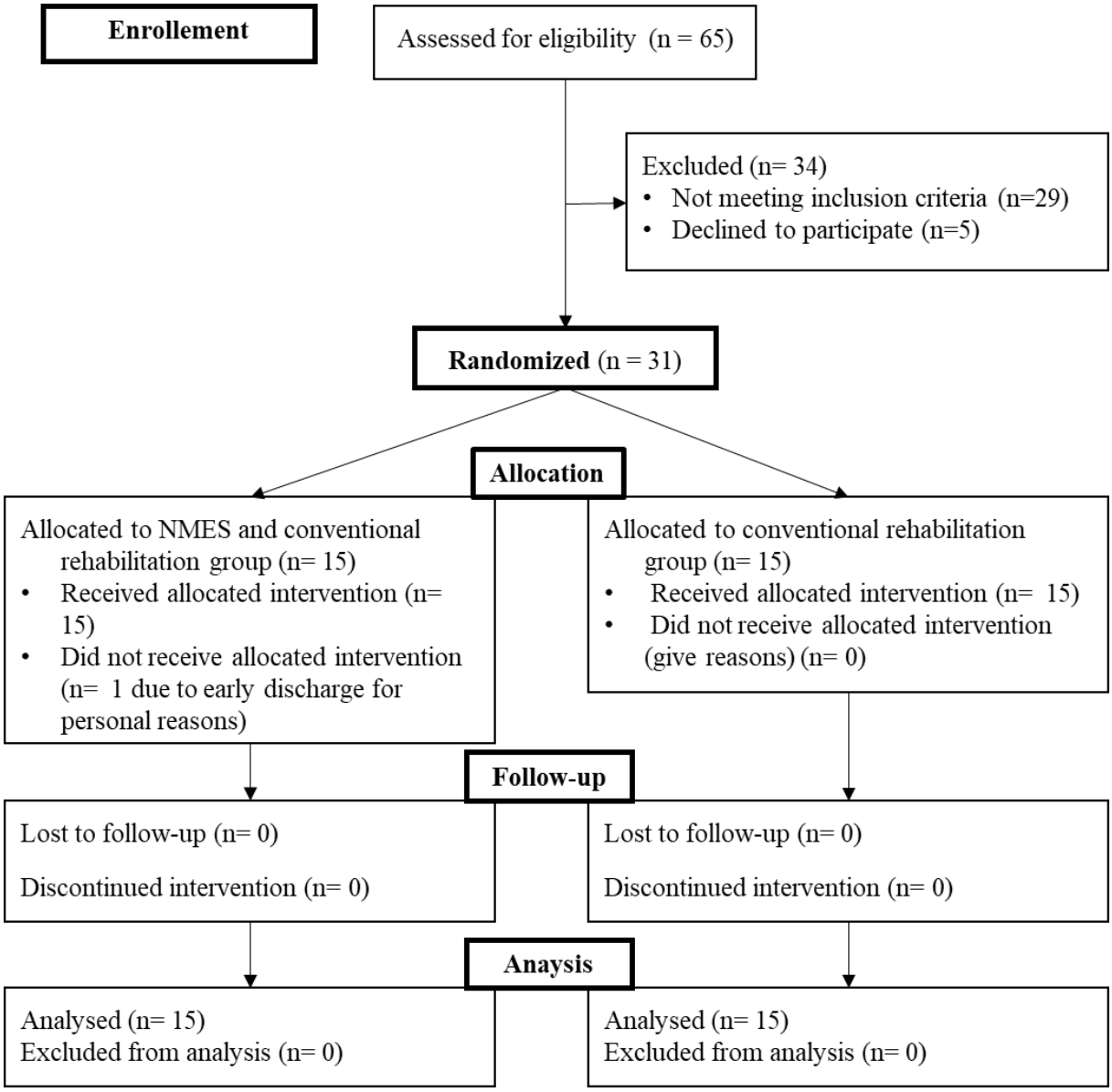

Figure 1. CONSORT flow diagram of the trial.

Effects on functional capacity

Functional capacity assessed by the 6MWT was significantly improved in the group of patients with NMES therapy (Table 2) compared to the control population (p=0.036). Regarding the NT-proBNP values, no statistically significant differences were observed between the two groups at the end of the study (NMES group 2138 (100 – 20230 pg/mL *vs*. control group 2518 (139 – 16015 pg/mL, p=0.95).

Table 2. Functional capacity in the analyzed patients with HF.

	Control Group		NMES group		P value
	Before	After	Before	After	
6MWT (m)	278.44±40.44	384.33±39.92	243.33±37.80	489.33±26.01	0.036

Effects on oxidized LDL

The oxidized LDL value showed a decreasing trend compared to the admission value in the group with NMES therapy, but without statistical significance (44 (24 – 358) ng/mL vs. 56 (20 – 491) ng/ml, p = 0.48).

Follow-up

At 30 days, 6 patients in both groups suffered a major adverse event, defined as HF hospitalization or death, 5 in the ESNM group and 1 in the control group, but without statistical significance (p = 0.17).

3.2. DISCUSSION

The main result of our study was the significant improvement of walking distance measured with the 6MWT in the group of patients with NMES admitted for AHF, an area covered by only a few trials until recently. Similar findings were presented by previous studies that evaluated hospitalized patients with advance HF [28, 29]. Compared with other studies performed on hospitalized HF patients the duration of NMES therapy in our report was shorter, approximately one week vs. 2 weeks [30, 31]. The increase in walking distance even after a short period of NMES therapy may be evidence that it counteracts the loss of muscle mass and exercise intolerance, aggravated by immobilization.

The present study provides evidence on the efficacy and safety of NMES therapy used early in hospitalized patients with AHF and a LVEF below 50%. This fact is of particular importance because, for safety reasons, conventional rehabilitation based on physical effort is applicable only to stable NYHA II or III class patients. There is evidence supporting the hypothesis that, for patients with HF, cardiac rehabilitation programs based on physical exercise decrease the oxidative stress and the plasmatic levels of oxidized LDL, suggesting an antioxidant effect of physical exercise. Thus, we studied the effects of NMES therapy on the plasmatic level of oxidized LDL, an indirect marker of oxidative stress, but we did not find any statistically significant change. We suggest as a possible explanation the fact that the duration of the therapy was too short to generate effects on the oxidative stress such as the improvement of the endogenous antioxidant system, which is reflected indirectly on the plasmatic levels of oxidized LDL.

There is little data in the literature regarding the effects of NMES therapy on oxidative stress. Gondin et al. showed in a study published in 2011 that NMES therapy improved the function of the antioxidant system in a healthy young male population [32]. Mancinelli et al. concluded that NMES is effective in producing physiological adaptation to the vastus laterals muscle in a population of healthy elderly patients without increasing oxidative stress at the muscle level [33]. Both of these studies used an electrical pulse frequency of 75 Hz, higher than the one used in out trial. We will monitor the population included in the study for major adverse events, considering the higher number of patients in the NMES group who have suffered a hospitalization for HF event or death.

Limitations: This study has the following limitations. First, there was no placebo NMES procedure in the control group. In this study we followed the immediate effects and the possible long-term benefits require further evaluation. We enrolled a relatively small number of patients in a single hospital, thus the generalization of the results found may have some limitations.

4. CONCLUSION

NMES therapy seems to be ideal for patients with AHF who are not currently able to follow a cardiac rehabilitation program based on physical effort, also considering the negative effects of prolonged immobilization on skeletal muscle during hospitalization. In this regard, this paper shows that for patients with AHF the NMES therapy used for a short term and initiated early during the hospitalization period improves exercise tolerance, suggesting the importance and possible necessity of including it as standard cardiac recovery therapy. The present study provides additional evidence regarding the safety of early-onset NMES therapy in a fragile group of patients such as those with AHF as well as those with intra-cardiac devices. NMES performed for approximately one week did not influence the plasmatic value of oxidized LDL.

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