Original Article

The effect of low frequency neuromuscular stimulation on sympathetic activity in advanced heart failure

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ABSTRACT

Aim of the study: The study was designed to determine the effect of low-frequency neuromuscular stimulation on sympathetic activity in advanced heart failure. Patients and methods: In this study, thirty patients with advanced heart failure (NYHA class IV) and mean± SD age of 56.13±1.13 years were included. They received 8 weeks (4 times/week) of increasing amplitude low-frequency neuromuscular stimulation on calf and quadriceps muscles after a thorough assessment of ejection fraction, Norepinephrine levels, 6-min walk test, and assessment of disability via Minnesota Living with Heart Failure Questionnaire. Results: Statistically significant decline was observed in sympathetic activity by Norepinephrine levels associated with decreased disability, with an improvement in ejection fraction, the change percentage in ejection fraction was 3.64% ($p=0.018$), with a decline in norepinephrine by a change percentage of -9.28% ($p<0.001$), associated with an improvement in six-minute walking test by a percentage of 22.97% ($p<0.001$) and improved psychological, emotional, and functional status of the patients with a decline of Minnesota Living with Heart Failure Questionnaire score by -24.06% ($p<0.001$). Conclusion: Low-frequency neuromuscular stimulation altered sympathetic activity leading to higher functional levels.

Keywords: Norepinephrine, Low-frequency neuromuscular stimulation, Muscles,Ergoreflex.

Introduction

Heart failure (HF) is a syndrome considered to be the final common way for many patients with cardiac disease and is associated with a low level of exercise capacity, poor quality of life, and depressive symptoms. Moreover, HF is characterized by overactivity of the neurohormonal system and endothelial dysfunction.[1, 2]

Despite the diversity of sympatho-excitatory mechanisms engaged in heart failure aiming at the preservation of cardiac output, it arises primarily from altered Norepinephrine kinetics, which is evidenced by increased plasma Norepinephrine levels with an elevated central sympathetic outflow.[3]

A hypothesis has developed, which explains this abnormal response to an exaggerated reflex known as ergoreflex developing with peripheral muscle abnormalities in chronic heart failure. When the skeletal musclebecomes abnormal in heart failure (HF), it would show changing patterns of the cardiorespiratory control, manifested in symptoms such as dyspnea, fatigue, and increased ventilation, usually reported by HF patients.[4]

According to such a hypothesis, it would be more suitable and effective to treat the cause, the musculoskeletal abnormalities, instead of managing the consequences of ergoreflex activation, such as sympathetic activation and peripheral vasoconstriction. Randomized and controlled studies have shown that physical training increases oxygen consumption and improves the neurohormonal balance in heart failure (HF).[1, 5, 6]

Physical training, which would affect the muscle tremendously, can be an integral part of the therapy in the patients.[7] However, these interventions are usually only appropriate in patients with

Access this article online	
Website:www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Donia M Elmasry, Nesreen G. Elnahas, HazemKhorshid, Awny F Rahmy.The effect of low frequency neuromuscular stimulation on sympathetic activity in advanced heart failure. J Adv Pharm Edu Res 2019;9(4):29-35.
Source of Support: Nil, Conflict of Interest: None declared.

moderate symptoms. Patients with more advanced CHF are often excluded due to excessive symptoms and dyspnea.[4] Therefore other interventions are recommended to cause muscle alteration without cardiac strain, in fact, Electrical Muscle Stimulation (EMS), in particular Low-frequency Neuromuscular stimulation (LF-NMES), has been proposed as an interesting alternative to interval training, since it is simple, well tolerated by patients with CHF, and produces an intense exercise stimulus to the peripheral muscles with low cardiac demand.[8]

Patients and Methods

Participants

Thirty patients with symptomatic heart failure (New York heart association class IV) with systolic left ventricular dysfunction (≤ 35% left ventricular ejection fraction (LVEF) were included in this study. Twenty-eight of these patients fully completed the study. None of thepatients participated in the rehabilitation programs prior to the study. The exclusion criteria included pacemakers, chronic obstructive pulmonary disease, other disorders and conditions that limited lower limb electrical stimulation (for example, burns, fractures, fixation), pre-existing neuromuscular diseases (for example Myasthenia Gravis) and presence of edema or subcutaneous fat that interfered with the application of neuromuscular stimulation. The purpose, nature, and potential risk of the study were explained to all patients. All patients signed a consent form prior to participation in the study. All patients were evaluated by echocardiography evaluated by 2D Simpson method, blood testing for norepinephrine levels, six-minute walk test (6MWT) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) before and after treatment.

Norepinephrine assessment

Patients were asked to stop Caffeine, such as coffee, tea, cocoa, and chocolate two days before the test. Patients were asked not to smoke four hours before the test. Norepinephrine pre- and post-baseline level were measured on days separate from LF-NMES.

Six-Minute Walk Test

Patients were asked to walk along the marked distance as far as they could, they were encouraged to continue walking but allowed to rest when needed without stopping the stopwatch.[9]

Minnesota Living with Heart Failure Questionnaire

MLHFQ was completed in the same environment. It was crucial to explain to the patients why it was important to collect their opinionsto reduce the number of missing data and therefore maximize the quality of the data collected. The Questionnaire was completed at the beginning of the study and re-evaluated at the end of the study.

The protocol of low-frequency electrical stimulation

All patients were instructed to wear loose, short clothes for the lower limbs; they were rested in a sitting position. The stimulated muscles were the quadriceps and calf muscles of both legs. Self-adhesive surface electrodes 50 × 90 mm and 50 × 45 mm "for proximal end of Achilles tendon (Fisioline self-adhesive and conductive electrodes) were positioned on the thighs approximately 5 cm below the inguinal fold and 3 cm above the upper patella border; for the calf muscles the electrodes were positioned approximately 2 cm under the knee joint and just over the proximal end of the Achilles tendon. Electrical stimulation was performed 60 min/day, 4 days/week for 8 consecutive weeks. The stimulator delivered a biphasic current of 15 Hz frequency. The current characteristics were set up as follows: "on-off" mode stimulus (20s stimulation, 20s rest), pulse width 200 ms, rise and fall time 1s, and maximal stimulation amplitude 65 mA. The first session of stimulation was started at lower amplitudes (≈30 mA) and gradually increased by 10-15 mA/day over the following 2-4 days until the final value of 65 mA was achieved, which was well tolerated by the patients.[10]

Statistical analysis

Data obtained prior and after management including ejection fraction, norepinephrine levels,6MWT, and questionnaire score were statistically analyzed and compared using SPSS software.

Results

Demographic data

The study included 30 men with mean age (±Standard Deviation) of 56.13±1.13 years, their weight ranged from 60 to 90 with mean weight (±SD) of 76.10±2.42 Kg, their height ranged164-189 cm with mean height (±SD) of 177.53±1.83 cm, their BMI ranged between 21.01-28.72 with mean BMI (±SD) of 24.04±0.67 as shown in table (1)

Ejection fraction

Ejection fraction before treatment ranged from 18% to 33% with mean value (±SE) of 24.73±1.55%. These values changed after treatment to range from 19% to 35% with mean value (±SE) of 25.63±1.58% (p=0.018). The percentage of improvement in the change in ejection fraction was 3.64% ↑.

Norepinephrine

Norepinephrine before treatment ranged 223-1040 pg/ml with mean value (±SE) of 792.10±59.87pg/ml. These values changed after treatment to 548-989 pg/ml with mean value (±SE) of 718.59±40.73 pg/ml (p<0.001). The percentage of change in Norepinephrine was -9.28%↓.

Six-Minute Walk Test

6MWT before treatment was 189-314m with mean value (±SE) of 238.57±11.66 m. These values changed after treatment to a range of 209-410 m with mean value (±SE) of293.37±16.23 m ($p<0.001$). The percentage of improvement in the change in 6MWT was 22.97%↑.

Minnesota Living with Heart Failure Questionnaire

The questionnaire score before treatment was 60-98 with mean value (±SE) of 81.87±3.78. These values changed after treatment to 24-79 with mean value (±SE) of 62.17±4.77 ($p<0.001$). The percentage of change in the questionnaire was -24.06 % ↓.

Correlation of the studied parameters

Positive statistically significant correlations were observed between pre-EF% and 6MWT with r-valueof 0.658 and $p<0.001$ (figure 1), while negative statistically significant correlations were found between pre-EF% and NE r- and p-value (-0.818) and $p<0.001$ figure 2 and pre-EF% and pre-MLHFQ r-valueof -0.851figure 3).

Negative statistically significant correlations were found between post EF% and NE with an r-valueof -0.622 and $p<0.001$ figures (4) and post EF% and post MLHFQ r-valueof -0.384 and $p<0.036$, figures (5).

A positive statistically significant correlation was observed between pre-NE and MLHFQ with an r-valueof 0.661 and $p<0.001$, while a negative statistically significant correlation was observed between pre-NE and 6MWT with r-valueof -0.431and $p<0.017$ (figures 6 and 7).

A positive statistically significant correlation was observed between post-NE and MLHFQ with r-valueof 0.458 and $p<0.011$ (figure 8).

A negative statistically significant correlation was found between pre-6MWT and pre-MLHFQ with r-valueof -0.614 and $p<0.001$ (figure 9).

A negative statistically significant correlation was found between post 6MWT and post MLHFQ with r-valueof -0.562 and $p<0.001$ (figure 10).

Table 1: Descriptive and comparative analysis of the mean values of the studied parameters measured throughout the study.

Measured parameter	Mean ± SE		Percentage of change	P-value
	Pre	Post		
EF %	24.73±1.55	25.63±1.58	3.64	0.018*
Norepinephrine	792.10±59.87	718.59±40.73	-9.28	<0.001**
6MWT	238.57±11.66	293.37±16.23	22.97	<0.001**
MLWHFQ	81.87±3.78	62.17±4.77	-24.06	<0.001**

Data expressed as mean ± SE value.

**p<0.001=highly significant, p<0.005= significant, p>0.005= non-significant; EF: Ejection Fraction, 6MWT: six-minute walk test, MLWHFQ: Minnesota Living with Heart Failure Questionnaire SE: standard error.

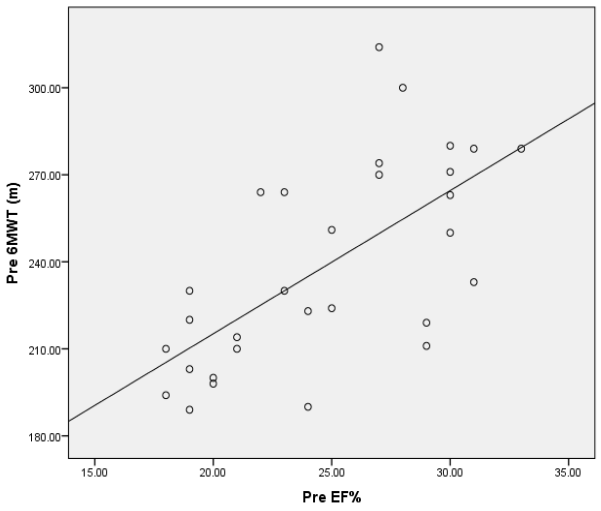

Figure 1: Scatter plot between pre-EF% and pre-6MWT (m).

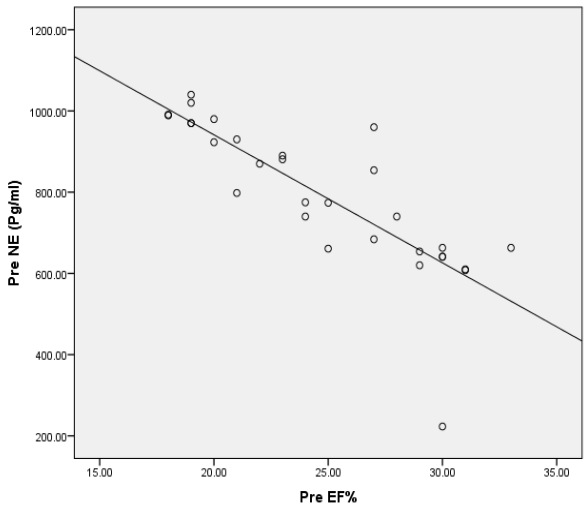

Figure 2: Scatter plot between pre-EF% and pre-NE (pg/ml)

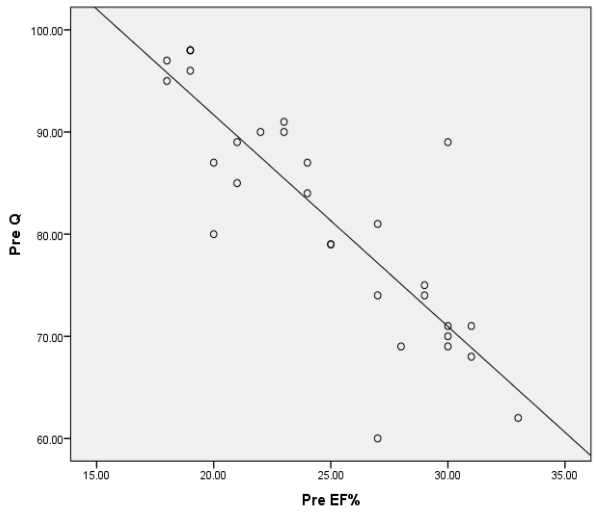

Figure 3: Scatter plot between pre-EF% and pre-Q

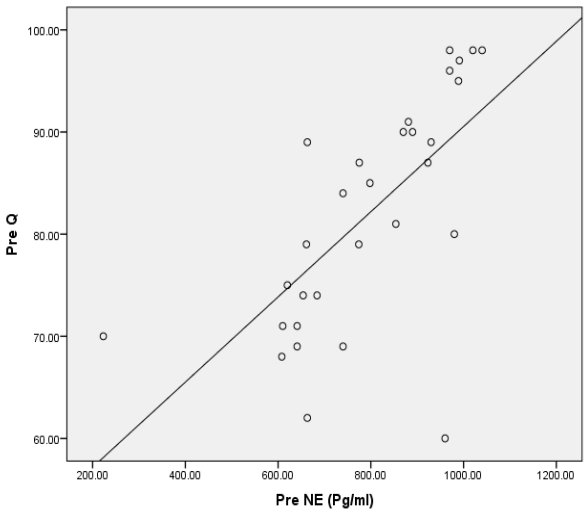

Figure 6: Scatter plot between pre-NE and Pre-Q.

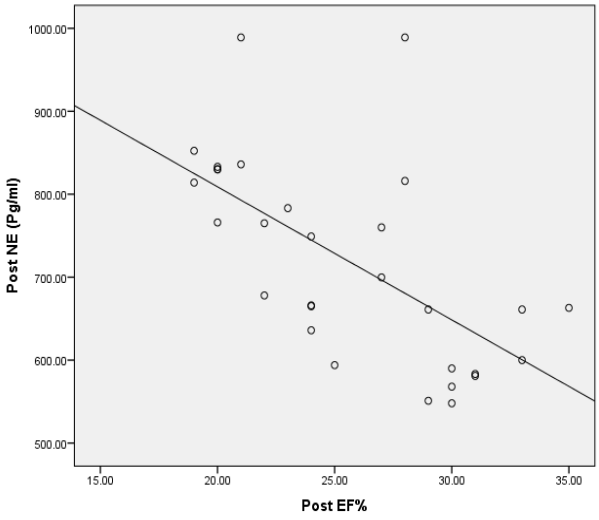

Figure 4: Scatter plot between post-EF% and post-NE (pg/ml).

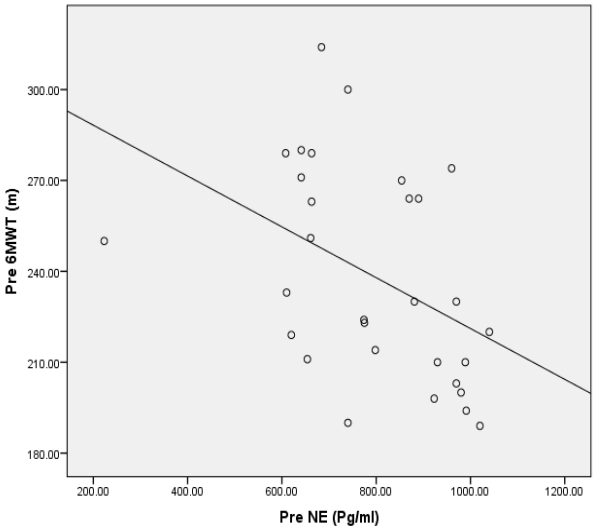

Figure 7: Scatter plot between pre-NE and Pre-MWT

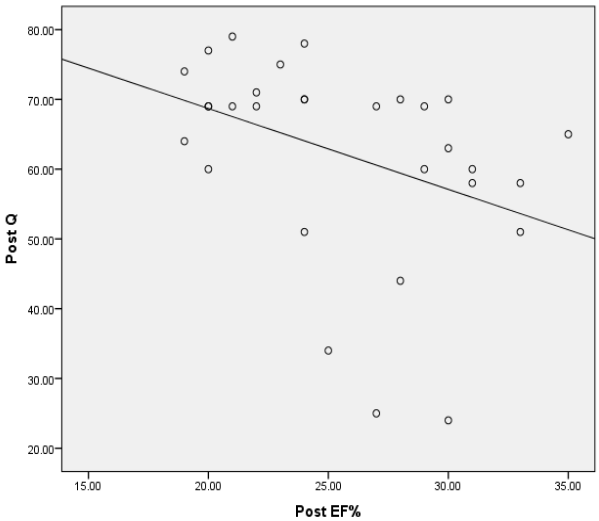

Figure 5: Scatter plot between post-EF% and Post-Q.

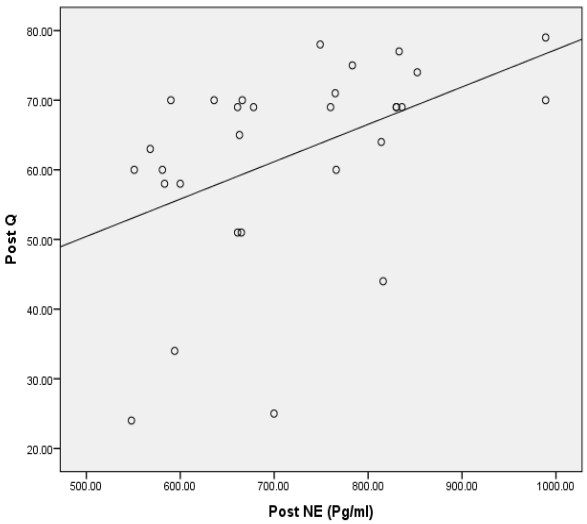

Figure 8: Scatter plot between post-NE and Post Q.

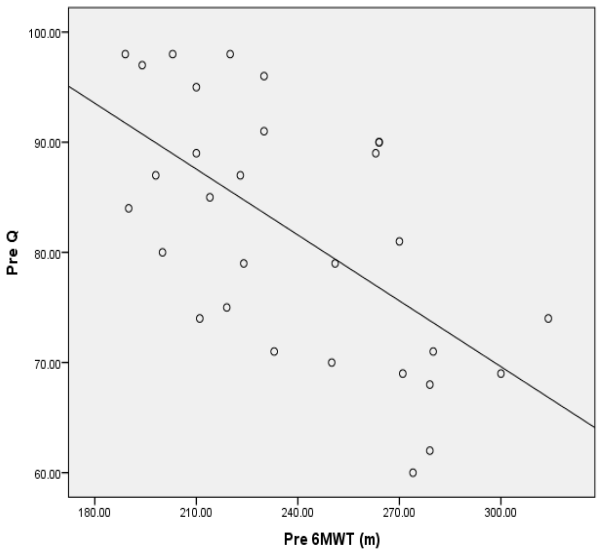

Figure 9: Scatter plot between pre-6MWT and pre-Q.

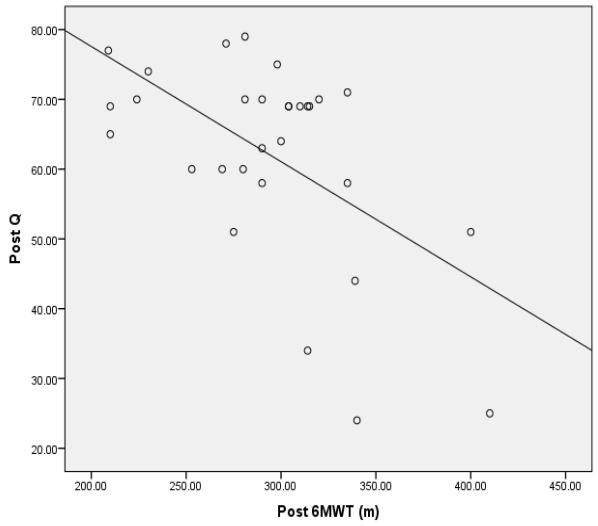

Figure 10: Scatter plot between post-6MWT and post-Q.

Discussion

Patients with chronic heart failure (CHF) are significantly limited by symptoms of fatigue and breathlessness. One proposal to explain the pathophysiology of symptoms is the muscle hypothesis is that peripheral skeletal muscle, which becomes abnormal in heart failure, is the source of the signals, which disrupts normal patterns of cardiorespiratory control through an increased sympathetic tone.

Sympathetic hyperactivity has been associated with poor prognosis in HF patients. In a classic study, Cohn and collaborators demonstrated that plasma norepinephrine concentration guides prognosis in chronic HF patients. Thus, approaches to reduce sympathetic activation are of great interest in the treatment of chronic HF. [11]

The aim of the present study was to test whether Low-frequency Neuromuscular Electrical Stimulation is able to safely correct exaggerated sympathetic activity in thirty patients with advanced heart failure; thus improving their constant sense of fatigue, increasing dyspnea, and exercise intolerance, and therefore might be used as a treatment alternative to exercising in such advanced conditions.

The current study demonstrated that 8 weeks of LF-NMES caused a significant modification of sympathetic activity evidenced by Norepinephrine level changes with a corresponding improvement in physical, functional, emotional, and psychological aspects of the patient performance combined with a significant effect on ejection fraction.

In the present study Norepinephrine baseline levels (measured on separate days before and after LF-NMES protocol implementation) showed a highly significant decrease accompanied by a considerable increase in ejection fraction. Alteration in norepinephrine levels was associated with a significant improvement in quality of life demonstrated by a decrease in MLHFQ and a highly statistically significant increase in 6MWT.

Studies that evaluated changes in sympathetic response inform the norepinephrine changes. The results of the study on the sympathetic activity may be attributed to the expected changes caused by the use of an eight-week program of LF-NMES, such as anergoreflexmodulation, changes in skeletal muscle fiber distribution, greater oxygen uptake kinetics, thus, decreased sympathetic hyperactivity.

The results of our study are consistent with the results achieved by Khorshidet al., where the ventilatory variables of ergoreflex were modulated in thirty patients with Advanced Heart Failure after being submitted in an eight-week program of LF-NMES. In the study patients received eight weeks of increasing amplitude low-frequency neuromuscular stimulation on Quadriceps and calf muscles after a thorough assessment of ergoreflex, ejection fraction and assessment of disability via MLHFQ, showing a statistically significant alteration of ergoreflex contribution associated with decreased disability withno statistically significant change in ejection fraction. The percentages of changes in minute ventilation (VE) and carbon dioxide production (VCO_2) and maximum oxygen consumption (VO_2) were 37.83%, -36.38%, and 25.46%, respectively. These changes were associated with improved functional, emotional, and psychological status of the patients with a decline of MLHFQscore by -29.87%.[4]

Groehs et al., 2016 studied the effect of LF-NMES on sympathetic hyperactivity in advanced Heart Failure assessed was investigated by Sympathetic Muscle Activity via microneurography and blood flow using venous occlusion plethysmography and the results seemed to be consistent with our current study. In a study conducted by Groehs, thirty patients with class IV (NYHA) were submittedand then subjected to LF-NMES of both Quadriceps and Gastrocnenuis muscles. The blood flow and muscle sympathetic nerve activity were recorded by venous occlusion plethysmography and microneurography, respectively. Blood pressure and heart rate were evaluated on a beat-to-beat basis (Finometer), quality of life by MLHFQ, quadriceps muscle strength by a dynamometer, and exercise tolerance by 6-min walk test. LF-NMES significantly decreased the MSNA burst frequency (P= 0.002) and burst

incidence(P=0.04), and significantly increased leg blood flow (P<0.001) and leg vascular conductance (P<0.001), along with an increase in the 6-minute walking distance (P<0.001) and a significant increase in knee extensor strength (P<0.001).[11]

Moreover, the changes mentioned in our study are consistent with the results reached by Labrunée et al. investigating the effect of acute LF-NMES on sympathetic hyperactivity as assessed by Muscle Sympathetic Nerve Activity (MSNA) via stimulation of quadriceps and calf muscles, with a frequency of 25 Hz. The application of LF-NMES caused a significant decrease of the muscle sympathetic activity from 56±3.7 burst/min to 51.6±3.3 burst/min by the decreased percentage of -7.85%.[12]

Our study concurs with a research review by Kucio et al., on the application of NMES in class II, III, and IV Heart Failure patients. In the conducted research, large muscle groups of the lower limbs were stimulated. The research showed that the strength of stimulated muscles increased by approximately 11–20% in relation to the starting strength of the muscle. The observed improvement of muscular strength applies to both isokinetic and isometric contractions. It seems that these changes are caused by the increase in aerobic enzyme activity of skeletal muscles, which, in turn, leads to increased oxidative capacity. Moreover, it was observed through the biopsy procedure that due to the application of NMES, an increase in type I muscle fibers occurred, which proved the evident recalibration of the stimulated muscles for aerobic metabolism and endurance training.[13]

In the present study, a positive correlation was found between ejection fraction and 6MWT implementation of LF-NMES, however, a negative correlation was found between ejection fraction, norepinephrine levels, and MLHFQ reflecting physical, functional, emotional, and psychological aspects of Heart Failure before and after implementation of LF-NMES.

Another correlation was set in our study between norepinephrine values as a marker of Heart Failure status, 6MWT, and MLHFQ. Before protocol implementation, a positive correlation was found between norepinephrine levels and MLHFQ, which was found to be also positive after LF-NMES application, however, a negative correlation was observed between norepinephrine levels and 6MWTbefore the protocol implementation.

Emphasizing physical, functional, emotional, and psychological aspects of Heart Failure a correlation was drawn in the present study between MLHFQ and 6MWT, before and after LF-NMES showing a negative correlation.

The results of our study coincide with a study by Kucio et al., 2018 in which participants of NYHA class II and III heart failure were included in the study, undergoing 3 weeks of LF-NMES of quadriceps and triceps surae. The study showed a statistically significant increase in 6MWT from 375±72.32 m to 452.1±86.72 m, associated with a statistically significant increase in LVEF from 37.3±4 % to 39.3±4.16%. The results were associated with a statistically significant decrease in MLHFQ changing from a mean of 22.7±12.86 to a mean of 13.5±8.16.[14]

Our study also agrees with a study by Sacilotto et al., 2017, which included 28 patients with end-stage CHF treated with NMES as a training program, applied for 50 min to both Quadriceps femoral muscles twice weekly over seven weeks. Results showed an increase in 6MWT ($p = 0.02$) and MLHFQ ($p < 0.01$) showing an inverse correlation at the end of study.[15]

Conclusion

Low-frequency Neuromuscular Stimulation attenuated sympathetic activity contribution in advanced Heart Failure decreasing patients' physical, functional, emotional, and psychological disabilities, promoting a much more independent and functional lifestyle.

Low-frequency neuromuscular stimulation is a safe and effective rehabilitation protocol that could partially reverse the abnormal response to exercise in advanced heart failure patients helping in their symptoms and improved activities.

Conflict of interest

The author declares no conflict of interest.

Funding

This research receivedno specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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