UNIVERSITY OF MEDICINE AND PHARMACY

CRAIOVA

PhD STUDIES SCHOOL

PhD THESIS

- ABSTRACT -

EFFICIENCY AND SAFETY OF LOWER LIMBS MULTICHANNEL NEUROMUSCULAR ELECTRICAL STIMULATION IN PACIENTS WITH CARDIAC DISABILITY

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KEY WORDS: chronic heart failure, skeletal muscle, neuromuscular electrical stimulation, pacemaker, exercise tolerance

1. INTRODUCTION:

The PhD thesis tackles an interdiciplinary topic. We propose a different and highly present perspective on a chronic heart disease – the chronic heart hailure (CHF) – seen as a systemic disease, in which the skeletal muscle disorder is considered both the „*final common pathway*" toward installing the disability in this disease, but also the fundamental structure on which the medical rehabilitation process is based on. The multichannel neuromuscular electrical stimulation (mc-NMES) of the ambulation muscles is proposed as a therapeutic alternative to increase exercise capacity, in those patients who cannot achieve conventional training based on active physical exercise.

2. CURRENT STATE OF KNOWLEDGE

The section on „Current state of knowledge " contains a summary of recent data from the scientific literature with respect to many aspects of this work: limiting factors of exercise capacity in chronic heart failure, structural and functional alterations of muscles in CHF as well as the underlying factors, general aspects of neuromuscular electrical stimulation (terminology, recent physiological concepts, scope, methodology), cardiopulmonary exercise testing, general notions about pacemakers and continuous electrocardiographic monitoring(Holter ECG).

3. PERSONAL CONTRIBUTIONS

The second part of the thesis, „Personal contributions", has three-pronged approach comprising three independent trials (which have in common mc-NMES in patients with heart disease), whose results shall be completed to obtain the final answers. Each of the studies had specific goals and used distinct groups of patients.

THE FIRST STUDY.

The effects of lower limbs' multichannel neuromuscular electrical stimulation (mc-NMES) on cardiorespiratory parameters in patients with heart pathology

(cardiorespiratory response to mc-NMES)

The objective of this study is the appreciation of „safety" in NMES application, by detecting potential „adverse cardiac effects" by tracking changings in some hemodynamic, respiratory and electrocardiographic parameters during and after a session of mc-NMES. If the NMES of a large muscle mass (quadriceps, hamstrings, triceps surae bilaterally) in patients with cardiac diseases, may lead to a possible inappropriate systemic circulatory response, which may subject the patient with cardiac pathology to undergo a risk of acute cardiovascular event, was the question the present study tried to answer to.

Material and method. A number of 19 patients (a M/F ratio=7/12) with average age of 61,52 years (SD=17,53) were included in the study, after signing the informed consent. The patients participating in the study were diagnosed with heart disease: **1**) Ischemic heart disease (ECG signs of coronary ischemia – asymptomatic or clinically espressed) – 3 patients; **2**) Sequelae of myocardial infarction (Q wave on the ECG track) – 3 patients; **3**) Cardiac arrhythmias and conduction disturbances (in total: 13 patients); **4**) High Blood Pressure – 10 patients; **5**) Heart failure – 7 patients. Note that the number of diagnosis of cardiac disease does not correspond to the number of patients, because most patients had more than one

diagnosis of heart disease. We excluded from the study those patients: 1) whose cardiac medication has changed in the last 3 months, 2) with an acute coronary event within 3 months prior the study entryf and 3) patients with severe aphasias that made impossible either understanding the nature of the intervention, or provide a feedback on the treatment.

The stages of the study were:

In the first day of the study (the day prior to the mc-NMES application), for each patient enrolled in the study were installed: a three channels 24-hours Holter ECG monitor *(Holter Monitor DL900, Braemar, Inc, Eagan, Mn, USA*), a pulseoximeter and a blood pressure monitor (to measure systolic blood pressure-SBP and diastolic blood pressure-DBP). Note that mean arterial pressure value was approximated (MAP), using the formula: MAP= DBP + 1/3(SBP-DBP). Hemodynamic and respiratory parameters values obtained during this monitoring were considered and recorded as **"baseline values".**

In the first part of the second day**,** the patients underwent a multichannel neuromuscular electrical stimulation program, with a duration of 21 minutes (preseted), of the: quadriceps muscle – rectus femoris (bilaterally); hamstrings (bilaterally); triceps surae (bilaterally). We used a multichannel programmable stimulation device, with 6 channels of simultaneous stimulation *(Megasonic 313, Electromedicarin S.A., Barcelona, Spania*) and 12 electrodes having the dimensions of 90/60/2 mm fixed with rubber bands through a hydrophilic coating. We used a pre-installed three-phases work program, which works on the principle of physical exercise itself: phase 1(4 minutes) – „*warming up*" (frequency at 30 Hz), phase 2(15 minutes) – physical exercise itself –"*work*" (frequency at 65Hz) and phase 3(2 minutes) – relaxation – „*relaxation*" (frequency at 3Hz). Throughout the electrical stimulation the patients continued to be monitored with Holter ECG.

SBP, DBP, SaO_2 values and respiratory rate were measured every 10 minutes during this period and their average values were calculated.It was approximated also the value of MAP (according to the formula). Heart rate values (average, maximum, minimum) were obtained from the continuous ECG monitoring results. Measured values at this moment of the study were called and recorded as ***"mc-NMES values".***

For an hour after stopping the mc-NMES (second part of the 2^{nd} day), the patients continued to be monitored with Holter ECG and we measured the values of the same parameters, at the same time interval. These measured values were called " ***post mc-NMES values".***

By using the Holter monitor software, in each of the three phases of the study, we analyzed and compared the following electrocardiographic parameters (calculated on the same time intervals):

- The number of ventricular ectopic beats(VE), couplets, triplets, bigeminy, trigeminy, number of supraventricular ectopic beats(SVE), SVE runs (≥3) and heart rate (average, maximum, minimum)
- Heart rate variability (HRV) by some parameters of time and frequency domain (**RMSSD** as an index of the vagal tone; **HF** expressing the parasympathetic modulation and **LF** which can be influenced by both sympathetic component as well as the parasympathetic (partially) and the **LF/HF ratio** as an expression of the sympathetic/parasympathetic balance.

Results. Conclusions.

In this study, the application of NMES on large muscle mass (such as muscles involved in ambulation), did not affect in a major and acute manner the central hemodynamics and did not generate immediate risks for a patient with cardiac pathology. All patients had adequate cardiovascular responses

during mc-NMES and immediately afterwards and there were no signs or symptoms requiring its discontinuation. The values of **SBP, DBP, MAP, average heart rate, O_2 saturation and respiratory rate** have not changed significantly during/after applying mc-NMES, compared to the baseline levels. The application of mc-NMES did not generate cardiac arrhythmias and did not increase the number of preexisting ventricular arrhythmias. During the application of mc-NMES compared to the baseline time, it has been found **an increase in the parasympathetic component** of the vascular and cardiac innervation. Subsequent to the application of mc-NMES it has been found that there is a **downward** trend of the HRV components compared with the baseline values and with those obtained during the application of the mc-NMES, even though this difference is not statistically significant for none of the study times. This shows a downward trend in parasympathetic control of the heart with the predominance of the adrenergic one immediately after ceasing the application of mc-NMES, situation that was not associated with the increase in the number of cardiac ectopies or with changes of the hemodynamic parameters.

These results, even if only observational (without statistical support), have important clinical implications, requiring patient monitoring at the end of the mc-NMES application, with the cardiac auscultatory assessment and with the measurement of some hemodynamic parameters (blood pressure, heart rate). I recommend it especially in patients with predictible HRV disturbances: heart failure, post – acute myocardial infarction, stroke, cardiac arrhythmias and having various indications for mc-NMES application. In the same context, in such patients, it would be recommended that the begining of the physical therapy session (which may involve also voluntary isometric exercises whose cardiovascular response is wellknown) can only take place after a minimum clinical evaluation of such a patient. This is because in clinical rehabilitation practice, the association of NMES training with active physical therapy is a common situation.

THE SECOND STUDY

Lower limbs' multichannel neuromuscular electrical stimulation (mc-NMES) in patients with implanted cardiac devices (pacemaker)

The objective of the study is the appreciation (testing) of the compatibility between the lower limbs'mc-NMES and the implanted cardiac electronic devices (pacemakers) and the identification of any sign of acute interference of the NMES with the pacemaker function.

Note that this study was conducted as a pilot study, with a small number of patients, thus preventing statistical risk analysis,therefore being only a study appreciating the individual safety in the application of the mc-NMES.

Material and method. A number of 10 patients (male/female ratio=6/4) aged between 66 and 84 years, that carry pacemakers of various types (7 patients – bipolar pacemakers; 3 patients – unipolar pacemakers) and having various time intervals after the implantation, with different clinical indications for permanent pacing, were included in the study after signing the informed consent.

The testing was performed under continuous monitoring of the ECG and blood pressure, under the supervision of a cardiologist. We used the ECG module of a cardiopulmonary exercise testing device (*Quark C12, COSMED SRL - Italia*).

We used a mc- NMES device (*Megasonic 313, Electromedicarin S.A., Barcelona, Spania*), with surface electrodes having the dimensions of 90/60/2 mm, fixed with rubber bands on the skin. The stimulated muscle groups were : quadriceps bilaterally, hamstrings bilaterally and triceps surae bilaterally. The distance between the tip of the bipolar electrode of the pacemaker and the closest surface electrode was not less than 45 cm (the electrode on the left quadriceps muscle); the same distance was measured between the stimulating electrode on the left quadriceps muscle and the tip of the unipolar electrode.

To each patient we applied 3 consecutive protocols of NMES at 3 **different frequencies** of the stimulation current, frequencies that were considered representative for the 3 major objectives of a NMES program: **8 Hz –** the frequency used in NMES programs – type *„warm-up"* and *„relaxation",* **20 Hz –** frequency used in NMES programs – type „*endurance training",* **65 Hz –** frequency used in NMES programs – type „*strength training.* For each patient, we used both forms: *burst "on"* and *„burst "off"* of the stimulating current, in order to increase the variability of the stimulation protocols. The testing was performed without adjusting the level of nominal ventricular sensitivity of the pacemaker. The patients were monitored for clinical symptoms and possible dysfunction of the pacemaker during the entire test (ECG, pulseoximetry, BP). The intensity of the electrical current was increased gradually, with 5 mA every 20 heart beats, up to the maximum tolerated intensity or until the clinical or electrocardiographic signs of inhibition of the pacemaker. The blood pressure was measured every 2 minutes. It was monitored constantly the O_2 saturation. For safety reasons, a Holter EKG/24 hours monitoring was performed in all patients after the NMES procedure.

Results. mc-NMES was very well tolerated by all patients, allowing the progressive increase of the stimulation current intensity, without causing any clinical signs of interference with the pacemaker activity. Monitoring the heart rate, blood pressure and oxygen saturation showed no clinically significant changes during the application of a number of 41850 stimulus pulses to the 10 patients.

Although not associated with changes in patients clinical status, we identified on the ECG recordings during the mc-NMES, some modifications in the ECG tracks in two of the patients (having uni- and bipolar unicameral pacemaker type): shortening of the LRI (*Lower Rate Interval*) during the application of the NMES (possible mechanism of *asynchronous pacing* – VOO), lengthening of the LRI (*Lower Rate Interval*) possibly by mechanism of overdetecting (*oversensing)* of the extracardiac electrical activity, *failure to capture*. Compared with ECG tracks previous to the application of the mc-NMES and those of the Holter monitoring/24 hours subsequently, the ECG changes occured during the application of the mc-NMES appear to be caused by the mc-NMES procedure itself, so they were interpreted as signs of interference between the two devices used simultaneously. Note that in the case of the two patients who had the above mentioned changes, the pacemakers were subjected to a check in the clinic where these devices were implanted, not finding changes of their initial parameters .

Conclusions. Although is applied afar from the implanted electronic system, the mc-NMES on lower limbs (with the 6 protocols described) seem to interfere with the pacemaker function, even if these interferences did not caused hemodynamic changes and were asymptomatic. Especially in the absence of the „alert" symptoms, to minimize the risk of adverse clinical consequences, I consider necessary: 1) To avoid applying the mc-NMES on patients with implanted cardiac defibrillators; 2) To know as detailed as possible the characteristics of the pacemaker, especially on the polarity of the electrodes (the bipolar mode is less vulnerable to interference, compared with the unipolar one) and the sensitivity threshold (the higher it is, the probability of interference is less); 3) The precautions regarding the NMES itself. Thereby, the NMES electrodes should be placed as closed as possible from one another, in order to

reduce the size of the electric field; the use of *„burst off"* mode; when the *„burst on"* mode is preferred, the duration of the *„burst"* must not exceed 3 seconds; 4) The performance of an initial „**safety test**" by continuous ECG monitoring during the application of the NMES (as in this study), to exclude the individual risk of interference of the NMES with the pacemaker function.

-if during the safety test signs of clinical and ECG interference do not appear, the application of the NMES may be continued under medical supervision and, if possible, under continuous ECG monitoring. If this is not possible, it is recommended a periodically Holter ECG monitoring because the lack of interaction between the NMES and the pacemaker during the test procedure does not eliminate the risk of happening during the subsequent applications of the NMES.

-if during the safety test there are clinical and ECG signs of interference, I recommend the patient assessment in the clinic where the stimulation device was implanted, specifying the type of physical procedures (in this case NMES currents of low frequency), the application area, as well as the duration and frequency that is expected to be applied.

To minimize the risks and to profit **safely** from the beneficial effects of certain physical therapy modalities, I consider necessary the **strictly individualized approach of the patient who carries** a pacemaker, that addresses to a Medical Rehabilitation service for the application of such procedures. On this line, the collaboration (in an advisory purpose) between the clinics of Medical Rehabilitation and the implant Centers for pacemakers, may indentify those patients with real risk of exposure to a given physical therapy procedure and ensure the appropriate follow up for these patients.

To simplify this advisory process I have designed an **"*Assessment sheet of the pacemaker patient, for the application of the physical therapy procedures*"**, wich contains data regarding the type of the suggested physical therapy, certain features of the pacemaker, as well as the cardiologist observations regarding the application of that procedure. This sheet is to be validated.

THE THIRD STUDY

The effects of intensive and short-term application of lower limbs' mc-NMES in admitted patients with chronic heart failure (CHF)

This study is the first in Romania to propose the use of NMES as a method to increase exercise tolerance in patients with CHF who are intolerant to active physical exercise.

In the author's opinion, this is the first study in literature that proposes a protocol for implementing two-stages NMES in patients with CHF.

The objective of this study is tracking the effects of the lower limbs' mc-NMES in patients with CHF who have activity limitation due to the heart disease, represented by the decrease in exercise capacity. The hypothesis that is the basis of this study is that an „*intensive*" lower limbs' NMES training could be beneficial to the patients with this type of pathology, to improve some hemodynamics parameters, the 6 mwd and the cardiopulmonary exercise testing (CPET), without showing adverse effects. In order to create the „*intensive"* nature of the NMES application, we used:

- A simultaneous 6 channels NMES application, on the ambulation muscles (lower limbs) – the so-called *„multichannel neuromuscular electrical stimulation (mc-NMES)"*.
- Short durations of NMES (10 days, representing about 75 minutes of electrical stimulation/day; 12,5 hours in total of NMES), thereby increasing patient compliance to treatment. If the expected

results are positive, this type of therapy could be recommended, with the objective to increase exercise capacity in patients with such pathology who are hospitalized. Under the present legislation, the optimal duration of hospitalization is 12 days – in Medical Rehabilitation settings, 7 days – in Cardiology, 7 days – in Internal Medicine, 11 days – in Cardiovascular Medical Rehabilitation.

- The application of two types of NMES training (force/strength and endurance) knowing that both muscle performance parameters are affected in CHF.

Material and method. This is a prospective randomized controlled study, conducted in the Medical Rehabilitation Clinic of the Emergency University Hospital „Elias".

Inclusion criteria:

- Patients with stable, symptomatic heart failure, II-IV NYHA (New York Heart Association); the heart failure stability was defined as the absence of changes in medication in the last month prior the enrollment in the study;
- Left ventricular dysfunction documented by echocardiography;
- activity limitations, in the sense of dyspnea and fatigue at different levels of effort (as a consequence of the heart failure);
- Patients which did not previously follow a rehabilitation program for the heart failure, through the physical exercise.

Exclusion criteria::

- Patients with signs of acute heart failure;
- Unstable angina, myocardial infarction or severe arrhythmia, 3 month before the enrollment in the study;
- Respiratory, neurological, musculoskeletal or peripheral vascular comorbidities that may interfere with performing the cardiopulmonary exercise test.

After signing the informed consent, 23 patients were included in the study. At randomization, the patients were divided in two study groups, distinguished by the intensity of the electrical current used for neuromuscular stimulation:

- The NMES group ,comprising 12 patients followed a program of neuromuscular electrical stimulation on lower limbs muscles (bilaterally): quadriceps (bilaterally), hamstrings (bilaterally) and triceps surae (bilaterally). The intensity of the current was progressivelly increased until visible and palpable strong muscle contractionswere achieved.
- The ccontrol group (CG) comprised a total of 11 patients. In these ones, he stimulation intensity was increased to the „sensitive threshold", defined as the sensation of „tingling" without producing visible, palpable contractions.

At the enrollment and at the end of the study, patients in both groups received the following determinations:

- The 6 minutes walking test (6 mwd);
- Determination of serum CK (creatine phosphokinase) and LDH (lactate dehydrogenase)
- A symptoms limited Cardiopulmonary exercise testing (CPET), with tracking: the maximum oxygen consumption (VO_2max); *anaerobic threshold* (lactate threshold)(AT), power (Watts) peak

during the effort; exercise duration (seconds); hemodynamic parameters (resting heart rate/ maximum heart rate during exercise, resting SBP/maximum SBP, resting DBP/maximum DBP).

For the NMES we used a programmable multichannel stimulation device, with 6 channels simultaneous stimulation (*Megasonic 313, Electromedicarin SA, Barcelona, Spania*) and 12 electrodes with the dimensions of 90/60/2mm, fixed with rubber bands through a hydrophilic layer on the muscle groups: quadriceps (rectus femoris) bilaterally; hamstrings bilaterally and triceps surae bilaterally.

The stimulation was performed 2 times/day, 5 days aweek, 2 weeks in a row. Two protocols of NMES/day were applied, in the morning/afternoon. The two protocols differ by frequency of the stimulation (combined training – for strength and endurance):

- With frequencies of 20 Hz (endurance training)
- With frequencies of 50Hz (resistance/strength training)

The duration of an application was about 75 minutes for the two protocols of NMES (12.5 hours in total).

Results. We compared the initial values of the followed parameters (heart rate, heart rate reserve, SBP and DBP, the duration of the exercise, power, VO_{2peak}, anaerobic threshold, 6 minutes walking test – 6 mwd, maximum dyspnea on the Borg scale, the sensation of fatigue on lower limbs on the Borg scale), between the two groups were not found statistically significant differences ($p<0.05$). This shows that the initial level of cardiorespiratory fitness of these patients was similar in the two groups. Thus, at the enrollment in the study, the patients in the two groups had similar degrees of disability from the exercise tolerance point of view.

We found negative statistically significant, correlations, between the level of NYHA functional class and the initial value of the 6mwd ($p=0.048$). Such a correlation has not been found between the value of the NYHA class and the initial value of the VO_{2max} ($p=0.760$). There is a statistically significant correlation between the initial value of the VO_2 and the 6mwd ($p=0.038$).

Comparing the differences between the final and initial values of the measured variables, between the two study groups, we found statisctically significant changes for: exercise SBP ($p<0.001$), exercise DBP ($p=0.003$), exercise duration ($p<0.001$), maximum power reached ($p<0.001$), VO_{2peak} ($p<0.001$) and 6mwd ($p<0.001$).

During the study, there were no cases of aggravation of the heart disease that required changes of the medication type or dosage of administration. NMES was well tolerated, not occuring any case of skin or muscle injury during the application of this type of therapy.

Conclusions. The active exercise training brings considerable and proven benefits to the patients with heart failure, representing the basis for their medical rehabilitation , thus being recommended in all national and international guidelines that refer to this type of condition.

In patients who, for various reasons (severe dyspnea installed early during the effort, associated neurological and musculoskeletal conditions), do not tolerate this type of training, the one that uses neuromuscular electrical stimulation of the muscles involved in ambulation, appears to be a „*link bridge*" or/and an „*alternative therapy*" to an active physical exercise training. The inclusion of this type of therapy in the "*non-pharmacological*" treatment in patients with heart failure that cannot perform conventional training, can be initiated in the hospital. I subscribe to Smart's proposal addressing he subsequent approach (after discharge) of exercise training of the patients with HF:

- If and when the patient improves his level of fitness, as a result of mc-NMES (a possible evaluation criteria is the reduction of NYHA functional class, ex. from IV to III), can associate and replace mc-NMES training with conventional exercise with the ergometer bike.

What could be the „threshold" of the VO_{2peak} or the 6mwd announcing that the right time of transition to active exercise remains to be investigated. The same author proposes a threshold of $VO_{2vârf} \geq$ 10ml/kg/min or 6mwd ≥300 meters.

Although the results are only preliminary, the present study is the first in Romania to propose the use of mc-NMES as a method to increase the exercise tolerance in patients with heart failure and the second in literature using an *„intensive"* two frequency electrical stimulation (tetanical=50Hz and non-tetanical=20Hz).

Further studies are needed to confirm these results, in order to include mc-NMES in the clinical routine prescription in the cardiovascular rehabilitation medicine.

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