Electrical Stimulation of Skeletal Muscles

An Alternative to Aerobic Exercise Training in Patients With Chronic Heart Failure?

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SUMMARY

The aim of this study was to investigate whether electrical stimulation of skeletal muscles could represent a rehabilitation alternative for patients with chronic heart failure (CHF). Thirty patients with CHF and NYHA class II-III were randomly assigned to a rehabilitation program using either electrical stimulation of skeletal muscles or bicycle training. Patients in the first group (n = 15) had 8 weeks of home-based low-frequency electrical stimulation (LFES) applied simultaneously to the quadriceps and calf muscles of both legs (1 h/day for 7 days/week); patients in the second group (n = 15) underwent 8 weeks of 40 minute aerobic exercise (3 times a week). After the 8-week period significant increases in several functional parameters were observed in both groups: maximal $\dot{V}O_2$ uptake (LFES group: from 17.5 ± 4.4 mL/kg/min to 18.3 ± 4.2 mL/kg/min, $P < 0.05$; bicycle group: from 18.1 ± 3.9 mL/kg/min to 19.3 ± 4.1 mL/kg/min, $P < 0.01$), maximal workload (LFES group: from 84.3 ± 15.2 W to 95.9 ± 9.8 W, $P < 0.05$; bicycle group: from 91.2 ± 13.4 W to 112.9 ± 10.8 W, $P < 0.01$), distance walked in 6 minutes (LFES group: from 398 ± 105 m to 435 ± 112 m, $P < 0.05$; bicycle group: from 425 ± 118 m to 483 ± 120 m, $P < 0.03$), and exercise duration (LFES group: from 488 ± 45 seconds to 568 ± 120 seconds, $P < 0.05$; bicycle group: from 510 ± 90 seconds to 611 ± 112 seconds, $P < 0.03$). These results demonstrate that an improvement of exercise capacities can be achieved either by classical exercise training or by home-based electrical stimulation. LFES should be considered as a valuable alternative to classical exercise training in patients with CHF. (Int Heart J 2006; 47: 441-453)

Key words: Heart failure, Rehabilitation, Exercise, Functional capacity, Electrical stimulation, Strength muscle, Home-based training

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DYSPNEA and premature fatigue of skeletal muscles are common symptoms of reduced exercise capacity in subjects with chronic heart failure (CHF). CHF is a complex metabolic syndrome with impaired left ventricular function and poor prognosis.[1,2] Several studies have reported a strong increase of sympathetic activity, the onset of peripheral vascular remodeling, and skeletal muscle metabolic alterations in response to exercise.[3-7] Histochemical analyses have demonstrated extensive mitochondrial damage resulting in depressed activity of the oxidative enzymes.[8-10] An important contributor to the decondition in CHF is physical inactivity and, since exercise training has been shown to improve functional capacity, quality of life as well as muscle strength should be considered as an integral part of the therapy in such patients.[11-13] Most types of actual training protocols, however, are based on systemic exercises that result in increased cardiac workload.[14,15] This could lead to the onset of life-threatening side effects such as fatal dysrhythmias, and for this reason classical rehabilitation programs require medical supervision. Other issues related to the choice of adequate exercise therapy for such patients are the severity of disease, low exercise tolerance, and poor motivation to exercise. Accordingly, a number of new training alternatives have been investigated, such as physical low-intensity training,[16] or resistance training based on muscle build-up.[17,18] Low-frequency electrical stimulation (LFES) of the skeletal muscles has been shown to increase oxidative enzyme activity in skeletal muscle fibers, to enhance muscular regeneration, and to prevent atrophy.[19] Considering the dramatic pathophysiologic changes that occur in chronic heart failure, such as deterioration of the muscle mass, the therapeutic effects of LFES in chronic heart failure should be examined. The aim of the present study was to evaluate the possible benefits of LFES in patients with CHF, and to compare the results with those of conventional bicycle training.

METHODS

Thirty patients (7 women, 23 men, mean age, 56.3 ± 6 years) with stable chronic heart failure, NYHA class II-III, and a mean left ventricular ejection fraction (LVEF) of 34.7 ± 5% were randomly assigned to 2 groups; patients in the LFES group (n = 15) underwent 8 weeks of home-based low-frequency electrical stimulation (LFES) of the lower limbs, while those in the bicycle group (n = 15) performed 8 weeks of exercise bicycle training (Table I). Informed consent was obtained from all the subjects before their inclusion in the study. The study was approved by the local Ethics Committee, and conformed with the principles outlined in the Declaration of Helsinki and to the GCP guidelines of the European Community.

Table I. Characteristics of Patients Included in the Study

Women / men	7 / 23
Age	56.3 ± 6 years
Heart failure etiology (ischemic/nonischemic)	24 / 6
Mean body weight	84.6 ± 7.7 kg
BMI	28.3 ± 3.9
NYHA class (II/III)	22 / 8
Left-ventricular ejection fraction (%)	34.7 ± 5%
Treatment	* ACEI, diuretics, β-blockers

* pharmacologic treatment was not changed 2 months or later before the beginning of rehabilitation.

Inclusion criteria: The inclusion criteria were symptomatic stability, NYHA class II-III, identification of coronary stenosis by coronary angiography, LVEF < 40% determined by echocardiography, and optimized pharmacological treatment (unchanged 2 months before and throughout the study).

Exclusion criteria: The exclusion criteria were the presence of unstable angina pectoris, evolutive ventricular dysrhythmia, intermittent claudication, an implanted cardiac pacemaker, diabetes mellitus, and chronic broncho-pulmonary disease.

Training protocols:

Protocol of LFES application.

The quadriceps and calf muscles of both legs were stimulated. Self-adhesive surface electrodes 80 × 130 mm (PALS® Platinum, Axelgaard Manufacturing Co., Lystrup, Denmark) were positioned on the thighs approximately 5 cm below the inguinal fold and 5 cm above the upper patella border. On the calf muscles, the electrodes were positioned on an area approximately 2 cm below the knee joint and just over the proximal end of the Achilles tendon. Electrical stimulation was performed for 60 minutes per day, 7 days a week for 8 consecutive weeks, using a dual-channel battery-powered stimulator Elpha-II 2000 (DANMETER® A/S, Odense, Denmark). The stimulator delivered a biphasic current of 10 Hz frequency. The current characteristics were set-up as follows: "on-off" mode stimulus (20 second stimulation, 20 second rest), pulse width 200 msec, and maximal stimulation amplitude 60 mA. Before handing over the stimulators to the patients, they were instructed on the use of the devices and the placement of the electrodes. Stimulations were performed at home, in the supine position, and at the same time each day (10-12:00 AM).

Protocol of exercise training on bicycle.

Patients in the bicycle group performed standard exercise training on a bicycle (electromagnetically braked bicycle ergometer: MAGNITEK, Taipei). The

training protocol consisted of a 10 minute warm-up session and 40 minutes of intermittent aerobic training (5 minute warm-up without workload, 30 minutes of training consisting of alternating periods of 1 minute of work and 2 minutes without workload, and a 5 minute cool-down period without workload). The final phase was 10 minutes of relaxation in the supine position. The exercise workload was adjusted individually and performed at the level of the anaerobic threshold determined by spiroergometry under supervision of the medical staff (doctor, physiotherapist and nurse). The training sessions were performed 3 times a week (Monday, Wednesday, and Friday, at the same time - 10:00 AM), for a total period of 8 weeks.

At baseline and after 8 weeks of the given type of rehabilitation, all patients underwent a 6 minute corridor walking-test and spiroergometric test for the evaluation of exercise performance. Spiroergometry was performed by all patients according to the standardized protocol of Wasserman, *et al*.[20] The test was done at progressively increasing working rates (10 W/min) to the maximal tolerance level on an electromagnetically braked bicycle ergometer (MAGNITEK, Taipei). Blood gases were analyzed throughout the entire exercise period and the recovery period (5 minutes). Heart rate was monitored continuously using a 12-lead electrocardiograph (SCHILLER Co., Germany), and blood pressure was measured noninvasively every 2 minutes. The peak workload was recorded; oxygen uptake and carbon dioxide production were calculated breath-by-breath (CPX/D system, Medical Graphics Corporation, St. Paul, Minneapolis), interpolated, and averaged over 10-second periods. Peak oxygen uptake ($\dot{V}O_{2peak}$) and oxygen uptake at anaerobic threshold ($\dot{V}O_{2AT}$) were determined according to the method of Wasserman, *et al* (1999). All patients underwent two 60-minute applications of LFES at the clinic under medical supervision. Blood pressure and heart rate values were monitored during these periods in order to evaluate the reactions of the hemodynamic parameters to LFES. Next, during the period of home stimulation, patients visited the clinic once a week to check the stimulators and to measure resting values of blood pressure and heart rate. To assess the quality of life (QoL), all patients completed the Minnesota "Living with Heart Failure" questionnaire (21 items) at baseline and at the end of the study.

Statistics: All data are presented as the mean ± SD. Statistical analysis was performed using the paired Student *t* test to compare within-group values before and after rehabilitation, the unpaired Student *t* test for comparison between both groups, and the Mann-Whitney *U* test to compare unpaired abnormally distributed data. Differences between the 2 groups were tested using one-way ANOVA. A P value < 0.05 was considered significant.

RESULTS

Six minute corridor walking-test: The distance walked after 8 weeks of rehabilitation was significantly increased in both groups; in the LFES group from 398 ± 105 m to 435 ± 112 m ($P < 0.05$), and in the bicycle group from 425 ± 118 m to 483 ± 120 m ($P < 0.03$). There was no significant difference between the 2 groups (Figure 1).

Duration of exercise testing.

The duration of exercise during the control spiroergometric test was significantly prolonged after 8 weeks of rehabilitation in the LFES group (from 488 ± 45 seconds to 568 ± 120 seconds, $P < 0.05$), and also in the bicycle group (from 510 ± 90 seconds to 611 ± 112 seconds, $P < 0.03$); there was no significant difference between the 2 groups (Figure 2).

Peak oxygen uptake.

Both types of rehabilitation significantly increased the value of peak oxygen uptake after 8 weeks. The $\dot{V}O_{2peak}$ in the LFES group improved from 17.5 ± 4.4 mL/kg/min to 18.3 ± 4.2 mL/kg/min ($P < 0.05$), and in the bicycle group from 18.1 ± 3.9 mL/kg/min to 19.3 ± 4.1 mL/kg/min ($P < 0.01$). Comparison of the 2 groups showed that the magnitude of increase ($\Delta\dot{V}O_{2peak}$) was greater in the bicycle group (bicycle versus LFES group, $P < 0.04$; see Figures 3 and 4).

Oxygen uptake at anaerobic threshold.

The value of $\dot{V}O_{2AT}$ was significantly increased in the bicycle group (from 11.1 ± 3.8 mL/kg/min to 13.6 ± 3.9 mL/kg/min; $P < 0.01$); 8 weeks of LFES led also to an increase in $\dot{V}O_{2AT}$, however, the increase was not statistically significant (from 11.3 ± 3.1 mL/kg/min to 12.1 ± 3.5 mL/kg/min, NS). Comparison of

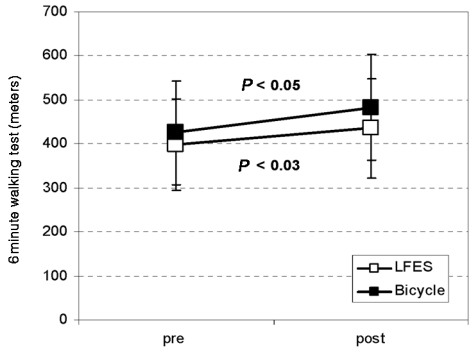

Figure 1. Results of the 6 minute corridor walking test in both groups at baseline and after 8 weeks of the given type of rehabilitation. Results are expressed as the mean (± SD).

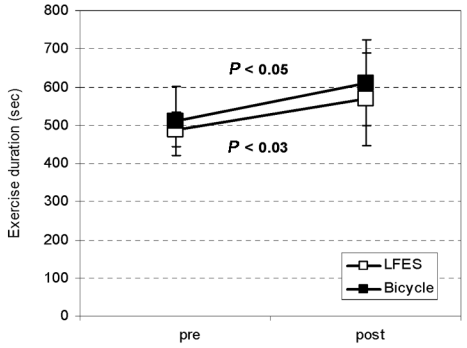

Figure 2. Results of exercise duration in both groups at baseline and after 8 weeks of the given type of rehabilitation (assessed by spiroergometric test). Results are expressed as the mean (± SD).

the 2 groups showed a significant increase in $\Delta\dot{V}O_{2AT}$ in the bicycle group (bicycle versus LFES group, $P < 0.02$; see Figures 5 and 6).

Peak workload.

Eight weeks of LFES significantly improved the values of symptom-limited workload in the LFES group (from 84.3 ± 15.2 W to 95.9 ± 9.8 W; $P < 0.05$); this parameter was also significantly increased in the bicycle group (from 91.2 ± 13.4 W to 112.9 ± 10.8 W; $P < 0.01$). Comparison of the 2 groups after 8 weeks of rehabilitation did not reveal any significant differences (Figure 7).

Peak heart rate.

After 8 weeks of rehabilitation the value of HR_{peak} increased significantly in the bicycle group (from 138 ± 28 beats/min to 159 ± 27 beats/min; $P < 0.03$). The

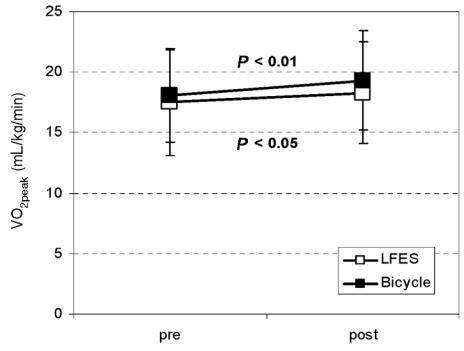

Figure 3. Results of peak oxygen uptake in both groups at baseline and after 8 weeks of the given type of rehabilitation (assessed by spiroergometric test). Results are expressed as the mean (± SD).

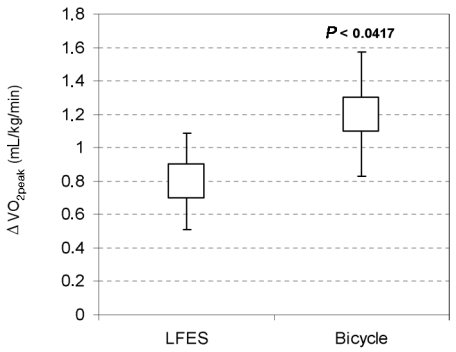

Figure 4. Increment of peak oxygen uptake ($\Delta\dot{V}O_{2peak}$); comparison of the 2 groups after 8 weeks of the given type of rehabilitation. Results are expressed as the mean (± SD).

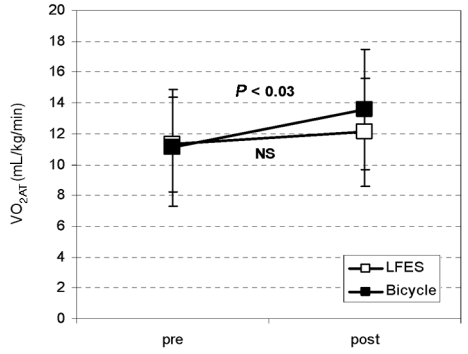

Figure 5. Results of oxygen uptake at anaerobic threshold (assessed by spiroergometric test) in both groups at baseline and after 8 weeks of the given type of rehabilitation. Results are expressed as the mean (± SD).

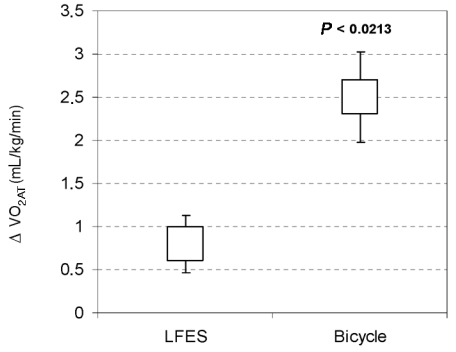

Figure 6. Increment of oxygen uptake at anaerobic threshold ($\Delta\dot{V}O_{2AT}$); comparison of the 2 groups after 8 weeks of the given type of rehabilitation. Results are expressed as the mean (± SD).

HR_{peak} in the LFES group was also increased, although not significantly (from 133 ± 31 beats/min to148 ± 22 beats/min; NS). There was a significant difference in ΔHR_{peak} between the 2 groups after 8 weeks of rehabilitation (bicycle versus LFES group; $P < 0.04$; see Figures 8 and 9).

Control blood pressure and heart rate monitoring.

No significant changes in systolic blood pressure (SBP), diastolic blood pressure, (DBP) and heart rate (HR) in comparison to the respective resting values were found in the two periods of stimulation during the control monitoring of the reactions of the cardiovascular parameters before the beginning of home stimulation (see Table II). As well, comparison of the mean resting values of SBP, DBP, and HR at the beginning and at the end of stimulation did not show any significant differences (values at baseline versus values after end of the stimulation

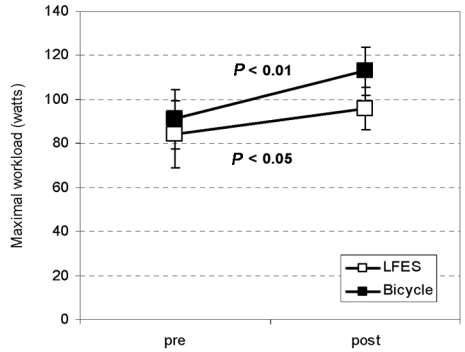

Figure 7. Results of peak workload (assessed by spiroergometric test) in both groups at baseline and after 8 weeks of the given type of rehabilitation. Results are expressed as the mean (± SD).

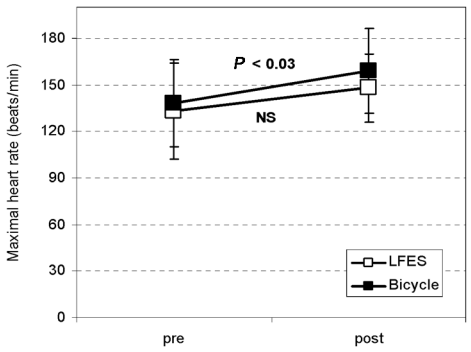

Figure 8. Results of peak heart rate in both groups at baseline and after 6 weeks of the given type of rehabilitation (assessed by spiroergometric test). Results are expressed as the mean (± SD).

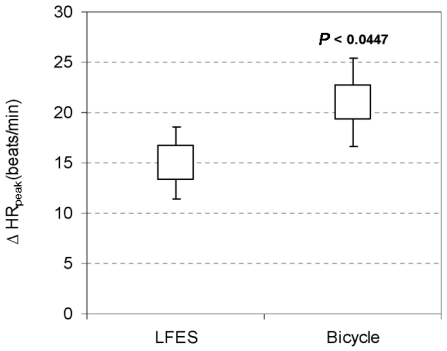

Figure 9. Increment of peak heart rate (ΔHR_{peak}); comparison of the 2 groups after 8 weeks of given type of rehabilitation. Results are expressed as the mean (± SD).

Table II. Comparison of Resting Input Values of Basic Cardiovascular Parameters at Rest and During 2 Control Applications of LFES Before the Beginning of Home Training

	At rest (baseline)	1. Stimulation	2. Stimulation	*P*
SBP (mmHg)	114 ± 5.8	119 ± 8.1	115 ± 5.9	NS
DBP (mmHg)	71 ± 6.5	77 ± 6.6	71 ± 8.4	NS
HR (bpm)	70 ± 3.8	76 ± 7.3	69 ± 3.1	NS

Results are expressed as the mean (± SD).

period: SBP 114 ± 5.8 mmHg versus117 ± 3.2 mmHg, NS; DBP 71 ± 6.5 mmHg versus 73 ± 5.3 mmHg, NS; HR 70 ± 3.8 bpm versus 71 ± 4.9 bpm, NS).

Quality of life score.

The QoL score assessed using the Minnesota Living with Heart Failure Questionnaire was significantly improved in the bicycle group (from 41.4 ± 5.3 to 27.3 ± 6.3; $P < 0.03$), whereas there was only a slight improvement in the LFES group (from 39.6 ± 2.9 to 31.4 ± 4.8; NS).

DISCUSSION

In the present study we have attempted to evaluate the therapeutic potential of low-frequency electrical stimulation (LFES) of leg muscles in chronic heart failure (CHF) patients. We demonstrated that LFES can effectively counterbalance their decreased physical capacity. The LFES protocol selected (frequency 10 Hz, stimulation 1 h/day, 7 days/week for 8 weeks) was very similar to that used by Maillefert, *et al*[21] who first reported a significant improvement of exercise capacity parameters in 14 patients with CHF after 5 weeks of LFES, namely an improvement of $\dot{V}O_{2peak}$, $\dot{V}O_{2AT}$, and a 6 minute walking test. In the same study, a nuclear magnetic resonance test showed a significant increase in the muscle mass of the triceps surae muscle. Similarly, Vaquero, *et al*[22] found a significant increase in the peak values of $\dot{V}O_{2peak}$ in CHF patients after 8 weeks of electrical stimulation of the lower limbs. The beneficial influence of LFES on muscle strength was reported by Quittan, *et al*.[23] Finally, 2 recent randomized trials showed that both home-based electrical stimulation of the legs and classical exercise training can significantly increase muscle strength and quality of life[24] and improve oxygen uptake after several weeks of stimulation in patients with CHF.[25] These results were confirmed also in the present study. The increases in $\dot{V}O_{2peak}$, W_{peak}, and distance walked in 6 minutes, and also the exercise duration after 8 weeks of LFES were very similar to the increases in these parameters in the bicycle group. Other parameters (HR_{peak}, $\dot{V}O_{2AT}$ and QoL) significantly increased in

the bicycle group but not in the LFES group (only slight improvement was observed). Comparison of the effectiveness of both LFES and bicycle training may lead to the conclusion that bicycle training is more effective at improving aero-metabolic capacity and heart rate response than electrical stimulation. On the other hand, the comparable increases in maximal workload, 6 minute walk-test, and exercise time in spiroergometric testing indicate similar effects on muscle endurance and resistance to fatigue in both groups. Despite the differences between the 2 methods (myostimulation activity is local, whereas bicycle exercise training challenges the entire body), LFES could be regarded as an acceptable analogue of endurance training which can improve the physiological condition of CHF patients in a period of several weeks, and can be easily performed at home without medical supervision. During the stimulation periods, no complaints were recorded concerning pain or health complications, such as skin burns or muscle damage. Similar experiences have already been reported in the studies by Harris, *et al*[24] and Nuhr, *et al*.[25] According to Maillefert, *et al*[21] and Quittan, *et al*,[23] LFES does not cause any significant change in cardiac output and heart frequency. During the 8 weeks of stimulation we did not observe any life-threatening side effects of LFES on blood pressure or heart rate. In our latest international trial, performed in a group of patients with advanced CHF (class NYHA IV, all on the "waiting list" for a heart transplant), only slight, insignificant increases in blood creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels were present after 1 week of stimulation. These findings could be explained as being a reflection of increased muscle load during introductory phases of stimulation, which resembles the increase in muscle activity in healthy people, for instance during exercise (unpublished observations). At the same time, this result suggests that stimulation does not cause any adverse overload of or damage to muscle fibers. The above cited results as well as our own experience during several years of application of LFES, justify the conclusion that the occurrence of life-threatening cardiovascular complications in CHF patients is minimal during stimulation of big muscle groups. We assume that LFES fully complies with strict methodological and safety criteria for application in CHF patients. This conclusion is supported by several electromyostimulation studies performed in CHF patients with implanted pacemakers.[26-28] It is well known that the global hypoperfusion and chronic hypoxia in CHF gradually damages the functional and metabolic integrity of the skeletal muscle mass. The consequent massive production of a variety of pro-inflammatory cytokines stimulates apoptotic pathways leading to fiber atrophy,[29] loss of strength, reduction of the total muscle mass, global overexpression of anaerobic white fibers (fast glycolytic), and the development of general cachexia.[30-34] A large number of studies have reported on the effects of LFES in mammalian skeletal muscles; the first pioneer work was done

40 years ago by A. J. Buller.[35] LFES in experimental animal models has been shown to induce qualitative and quantitative changes in different compartments of skeletal muscle fibers. Both structural and functional alterations observed might be caused by transformation of fast protein isoforms to their slow counterparts, followed by increased activity of oxidative enzymes, improved oxygen consumption and growth of the terminal micro-vascular bed, with increased expression of vascular growth factors.[36-38] These changes represent the basis for the general improvement of the aero-metabolic capacity, the prevention of muscle atrophy, and increased resistance to fatigue. Such events could play a very important role under the conditions of chronic heart failure characterized by impaired oxidative capacity and poor fatigue tolerance. Electrical stimulation of skeletal muscles in humans has been shown to be a useful therapeutic tool in neurology,[39-42] postoperative treatment, and in cases of long-term immobilization.[43-46] In a recent study, LFES was reported to improve the functional capacity in claudicants.[47] Hamada, *et al*[48] observed enhanced energy consumption, carbohydrate oxidation, and whole body glucose uptake after low-frequency electrical stimulation of the lower limbs, a finding that suggests the possibility of therapeutic application of LFES for diabetic subjects. However, the number of studies concerning the effects of LFES in cardiovascular rehabilitation is still very low. The effectiveness of conventional exercise training in cardiovascular rehabilitation has been sufficiently proven,[49-53] and LFES is not likely to replace it. But the safety and ease of application could be especially beneficial in patients with advanced CHF (III-IV). Although the present results are encouraging, it is necessary to take into account the limitations of this trial, for example the low number of patients included. Further investigations should yield more detailed data, including information about possible interactions between the central and peripheral cardiovascular mechanisms during muscle stimulation. Future studies should also address the possibility of combining LFES with some type of classical exercise training. Clinical trials in larger groups of patients will be needed before fully utilizing LFES in cardiovascular rehabilitation.

Conclusion: This study is among the first randomized trials aiming to compare the effectiveness of low-frequency electrical stimulation of skeletal muscles with conventional bicycle training in patients with chronic heart failure. The present results demonstrated the good tolerance and significant improvement of functional capacity after 8 weeks of electrical stimulation. It can be concluded that an improvement of exercise capacity in patients with chronic heart failure can be achieved either by aerobic training or by local electrical stimulation of the strength muscles of the lower limbs.

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