Strength Training – induced Left Ventricular Remodeling in Heart Failure Patients

Short Paper

Zahra Sadek, Said Ahmaidi
Laboratory EA 3300 (APERE) « Adaptations Physiologiques à l'Exercice et Réadaptation à l'Effort »
Picardie de Jule Vernes University
Amiens, France
Zahra.sadek@etud.u-picardie.fr
Said.ahmaidi@u-picardie.fr

Wissam Joumaa, Ali Salami
Laboratoire Rammal Hassan Rammal, équipe de recherche PhyToxE, Faculté des Sciences (section V),
Université libanaise, Nabatieh, Lebanon
wjoumaa@ul.edu.lb
a.salami@ul.edu.lb

Mahmoud Youness, Pierre Nassar, Righab Hamdan
Medical Research Center
Beirut Cardiac Institute
Beirut, Lebanon
Myouness55@yahoo.com
Nassar.pierre@hotmail.com
Mdrighabh@hotmail.com

Wiam Ramadan
Lebanese Institutes for Biomedical Research and Application (LIBRA)
International University of Beirut (BIU) and Lebanese International University (LIU)
Beirut, Lebanon
wiam.ramadan@liu.edu.lb

***Abstract*— The hypothesis tested in chronic heart failure patients with inspiratory muscle weakness demonstrates that the Resistance Training results in further improvements compared to control in terms of dyspnea, cardiac, skeletal and inspiratory muscle function and quality of life. Twenty patients with ejection fraction ≤45% and inspiratory muscle weakness described by maximal inspiratory pressure <70% predicted, had undergone 3 exercise training sessions per week for 12 weeks. Patients were randomly allocated to one of two groups: RT group or control group. RT performed at 60% of 1 repetition maximum. Control group patients had no training at all. At the beginning and the end of the study, patients underwent pulmonary function test, respiratory muscle function test, echocardiography, exercise test, skeletal muscle function test, 6 minutes' walk test and were evaluated for their quality of life using the Minnesota living with heart failure questionnaire. RT showed significant positive effects on ejection fraction, exercise test variables, functional capacity, respiratory muscle function, skeletal muscle strength and endurance as well as dyspnea and quality of life. Resistance training was superior to control in all parameters assessed, and most importantly in exercise time (68% versus 27%, P=0.008), respiratory muscle function (Maximal inspiratory pressure, 60% versus 14%, P=0.001; Sustained maximal inspiratory pressure, 71% versus non-significant improvement in resistance training group, P=0.022) and skeletal muscle endurance. However, no significants improvements were detected in control group patients. Resistance training has been applied to improve respiratory muscle strength in chronic heart failure patients. In addition, the resistance training was safe and resulted in additional benefits in cardiac, respiratory muscle and skeletal muscle function compared to the control.**

Keywords- Chronic Heart Failure; Resistance Training; Functional capacity; Skeletal Muscle Function; Respiratory Muscle Function; Ejection Fraction.

I. Introduction

Exercise intolerance, dyspnea and fatigue are the main obstacles that Chronic Heart Failure (CHF) patients face during their daily life activities [1]. These phenomena might contribute to physical impairment and result in a poor Quality of Life (QoL) [2]. Such restrictions happen as a consequence of reduction in skeletal muscle mass and strength, which might be explained by both qualitative and quantitative abnormalities [3]. In fact, there are histological and biochemical derangements expressed respectively by altered fibers distribution and reduced oxidative enzyme activity in addition to muscle metabolism impairment, mitochondrial changes, inflammation and muscle atrophy [4]. Skeletal muscle abnormalities are mainly characterized by muscle fiber type switch, fiber atrophy and muscle wasting, as well as the reduction in mitochondrial volume density and mitochondrial aerobic capacity [5–7]. Similar alterations have been detected in the respiratory muscle, with the exception of fiber type switch. In the peripheral skeletal muscles, the switch appeared to be in favor of type Ⅱb fast twitch fibers with low aerobic capacity that gets quickly fatigued [5] while respiratory muscles had a switch towards type Ⅰ slow twitch fibers [5]. After a period of intense evaluation of the safety and effectiveness of exercise rehabilitation in CHF patients, exercise training was shown to be the cornerstone of cardiac rehabilitation programs.

Because muscle dysfunction represents a hallmark of heart failure, the emphasis was on Resistance Training (RT), in order to restore the normal muscle structure and function [8]. For many years, bed rest and limited physical activity were recommended for all stages and forms of heart failure; while exercise was not suggested [9]. Nowadays, however, the concept of cardiac rehabilitation, including exercise training, and specifically RT, is well spotlighted and highly recommended recently, mainly because of studies that show its benefits in various outcomes [6]. In fact, application of such programs induces significant histological, metabolic and functional adaptations in skeletal muscles, thereby, improving patient's QoL. McKelvie was the first to demonstrate in 1995 that there are no significant differences between cycling and RT regarding left ventricle response in heart failure patients [10]. This study found similar results with those obtained from Meyer et al. where central hemodynamics was stable and well tolerated during resistance exercise [11]. In addition, from the research conducted by Grosse et al. who performed RT at 65% of 1 Repetition Maximum (RM), an increase of 80–102% of muscular endurance and 14.5% of VO2peak was reported [12]. Pu et al. who performed RT at 80% of 1RM, also showed a 43% and 13% increase of muscular strength and Six-Minute Walk Test (6MWT), respectively [13].

These findings are consistent with those of Levinger et al. who discovered 18% increase of muscular strength and 19% amelioration of VO2 peak after training patients at 40–80% of 1RM [14]. As shown above, the significant improvements in muscle strength and endurance, the adaptation of muscle mass and the increase in the QoL and functional capacity had been proved by many researchers after RT [11] [13] [14]. Each study performs RT according to specific characteristics such as intensity, duration, frequency, number of repetitions and sets of exercise. Overall, these features should be taken into consideration to avoid any cardiovascular stress, and thereby any harmful consequence. The aim of our study is to determine the effects of RT on skeletal and respiratory muscle function, functional capacity, cardiac function, dyspnea [15] and QoL in patients with CHF. The paper proceeds as follows: Section II describes the experimental design, data are analyzed in Section III, Section IV presents the discussion and, finally, Section V draws the conclusions.

II. METHODS

A randomized, single-blinded, parallel controlled study was performed in patients who were diagnosed with stable CHF and inspiratory muscle weakness (IMW) [maximal inspiratory pressure (MIP) <70% predicted] and recruited from Beirut Cardiac Institute. 53 patients were assessed for eligibility and 33 were excluded due to some limitations (figure 1). Eligible subjects [Ejection fraction (EF) ≤ 45%, NYHA class II or III, diagnosed with CHF for more than 6 months as long as there has been no admission to the hospital or any change in medications throughout the previous 3 months] were randomized to different exercising groups. Excluded subjects suffered from pulmonary limitation [Forced expiratory volume (FEV1) and/or vital capacity <60% of predicted], orthopedic or neurologic disease, had a history of significant cardiac arrhythmia, a history of myocardial infarction or a cardiac surgery over the past 6 months, non-echogenic, unstable, poorly controlled blood pressure and/or end-stage HF.

A written informed consent form was signed and obtained from all the participating subjects and all of them were receiving the same type of medication that included mainly beta blockers, Angiotensin converting enzyme inhibitors (ACE-I) or Angiotensin II receptor blockers (ARB) and Diuretics.

Furthermore, an approval for the experimental protocol was obtained from the Committee for Ethics in Research of Beirut Cardiac Institute. Since humans were included in this study, a certificate from the National Institutes of Health (NIH) for Protecting Human Research Participants (PHRP) was obtained. The patients received detailed information and gave written informed consent before their inclusion in the study.

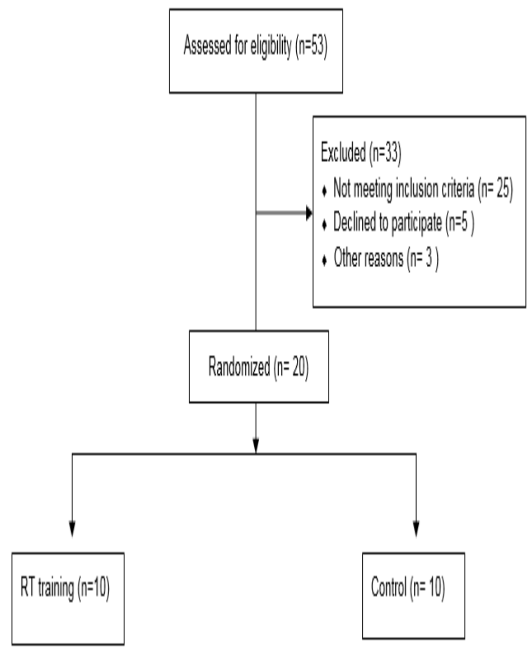

Figure 1. Flow chart of patient's recruitment.

20 subjects were block randomized with 1:1 to 2 groups as shown in the consort diagram in Figure 1. Randomisation was conducted by using a research randomiser web site (Scott Plous and Jeff Breil, Lancaster, Pennsylvania). The patients were divided, thereafter, into two different groups: controls (n=10) and resistance (n=10) for 12 weeks (3 times / week).

Demographic, clinical characteristics and drug therapy lists for all patients were collected at the beginning and the end of the study. Arterial blood oxygen saturation and heart rate (HR) were monitored using VIAMED pulse oximetry, and blood pressure (BP) was measured using a sphygmomanometer prior to the initiation and after the termination of each exercise session.

A. Cardiac Function

Echocardiography test: it is a test that makes an evaluation of the heart function possible. It creates images of the heart and helps in the analysis of different cardiac measures. Assessment of heart structure and function at rest was done using a Vivid S6 ultrasound probe (General electric healthcare GEMs supplies) where the patient was seated in a supine position. Two experienced cardiologists, blinded to subject's allocation and his/her study period, performed the test.

Measurements of ventricular volumes were assessed using the biplane method of disks (Biplane Simpson's method) from an apical 4 chamber view. Noting that this method is highly recommended for measuring the LVEF [16].

B. Exercise Test

Bruce treadmill protocol was used for the assessment of cardiovascular status during a progressive incremental exercise. Patients exercises on a treadmill with intensity and grade increasing progressively throughout the test following Bruce protocol. They also had ECG leads placed on their chests and a sphygmomanometer cuff for BP monitoring. Exercise time, grade, METs and BP were recorded during and after the test.

C. Lung Function

Pulmonary function was assessed using Digital Spirometer device. During this test, subjects were seated and instructed to inhale deeply through a mouthpiece well fitted between the lips and to exhale quickly and forcefully straight after. Air leakage was prevented by using a nose clip during the maneuver that was repeated three times to guarantee maximal performance.

The important parameters detected through this test were: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1 to FVC ratio.

D. Respiratory Muscle Strength

Respiratory pressure meter (MicroRPM carefusion), a portable hand-held device, was used to measure MIP and maximal expiratory pressure (MEP). The results of the test were displayed on a screen in cmH_2O. A PUMA PC Software that offers unique features could associate with the hand-held MicroRPM in order to improve its functionality. During this test, patients were instructed to tightly fit the mouthpiece attached to the instrument between both lips. Familiarization with the device and the ventilator operation was done before starting the test.

To measure MIP, the subject had to exhale to residual volume then perform Mueller maneuver characterized by a forceful inhalation against the instrument as long as possible.

To measure MEP, the subject must inhale to total lung capacity (TLC) and then exhale forcefully (Valsalva maneuver) over a minimum duration of 2 seconds. Both maneuvers were repeated at least 3 times in order to obtain the best values of MIP and MEP; noting that reported values were the maximum pressures sustained over a one second period.

E. Respiratory muscle endurance

To measure the endurance of the respiratory muscle, patients were instructed to breathe using Power Breathe set at 70% MIP/sustained maximal inspiratory pressure (SPI_{max}). The maximum time (in seconds) tolerated was recorded and meant to evaluate inspiratory muscle endurance, SPI_{max}/time. This test was repeated 3 times, with 1-2 minute rest intervals.

F. Leg Skeletal muscle function

Skeletal Muscle Strength Test: A handheld dynamometer (Lafayette instrument) was used to assess the skeletal muscle strength by measuring the force generated by the quadriceps. Because this device is portable and light, the examination procedure is made easier. Before the test, the subjects had been familiarized with the operative device and the intended protocol. Patients were placed in an upright seated position at a knee and hip angulation of 60° and 120° respectively. Verbal encouragement was used during the test period. Maximum voluntary isometric force (MVIF) in kg was measured; three sets of three repetitions were given to each patient to develop maximum force with a 20 second rest period between each set. MVIF was reported as the average of the nine values taken. Peak force, average force and peak time were recorded by the device and transmitted to the computer software.

Skeletal Muscle Endurance Test: 50% MVIF was used to assess skeletal muscle endurance. Patients were told to maintain 50% of the MVIF as long as possible until maximum tolerable elapsed time is recorded. The procedure was repeated three times separated by 5 minutes of rest. Endurance time was calculated as the average of the three sets. Verbal encouragement was given to patients before and during the test to achieve the best possible performance.

G. Physical Activity

Inclusion criteria for this study required that patients had a sedentary lifestyle to avoid bias since some patients might be following a specific activity program. Thus, in order to make sure that all the patients met the criteria, the short international physical activity questionnaire (IPAQ) [17] was used to assess the level of each patient's physical activity. The questionnaire was administered over the phone or during the first office meeting. It is made up of 7 questions the patients were asked to answer telling the time they spend doing an activity. The activities include those done at work, at home, yard work, exercise and others.

H. Functional Capacity

Functional capacity in CHF patients was predicted by using the 6 minute walk test (6MWT) [18], which is evidenced to be reliable and reproducible. The test was performed in a 60-meter corridor under the supervision of a physical therapist. Initially, patients had been familiarized with the corridor space and the time needed to complete the test. BP, HR, and arterial oxygen saturation were measured before and after the test. A stopwatch was used to record the elapsed time as soon as the subject's began the test. Patients were free to decrease their speed and stop if necessary. The test was repeated three times with 5 minutes of rest between sets.

I. *Dyspnea*

During each training session and during the exercise test, patients were asked to evaluate their exertion level using Borg scale [15].

Borg scale provides information about perceived exertion but nothing on the level of difficulty of the exercise. The scale is a set of different intensity levels, where patients evaluate their exertion level using an attached visual numerical scale of 6 to 20 with 6 corresponding to no fatigue or other symptoms and 20 to maximum exertion. Borg scale is known for its sensitivity and reproducibility to be used as a subjective reference during submaximal workouts [19].

J. *Quality of Life*

QoL was assessed using Minnesota living with heart failure questionnaire (MLwHFQ), which was approved for the use in clinical practice and research [21]. MLFQ has been translated into and approved in Arabic.

This questionnaire is composed of 21 items used to qualify physical and emotional aspects. A grading scale that evaluates the degree of HF impact on the QoL, with 0 (none) to 5 (very much), was used. Low scores indicate that patients had mild problems associated with HF and high scores indicate a high impact of HF on QoL. Introducing the questionnaire to the patients was easy and questions were answered clearly.

The information collected thanks to MLHFQ provided an overview about the physical, social and mental status of patients before and after the interventional process.

K. *Training programs*

Patients were randomly assigned into two groups. The training regimens were performed 3 times a week for 12 weeks.

Control: The control group included 10 patients who did not exercise at all and were instructed to continue their normal life activities during the three months of trial.

Resistance Training: Ten patients were included in the RT group. The training protocol encompassed strength exercises that targeted the muscles of the quadriceps, the hamstrings and gluteus muscles of the lower extremities; Biceps, Triceps, Deltoid and Pectoralis of the upper extremities.

A total of seven strength exercises were used to train the upper body and six strength exercises to train the lower body limbs. Each workout was composed of 3 sets and each set of 10 repetitions, with at least 15 seconds of rest between sets. The patients started training at 60% of 1RM that was assessed and recalculated every two weeks. All the patients started with 3 sets of 5 repetitions each but after the third session, all of them had completed the whole 3 sets with 10 repetitions each. The total training time was 30 minutes.

L. *Statistical analysis*

All continuous variables are expressed as mean ± standard deviation of the mean (m ± SD). Baseline comparisons among the groups were performed using one way ANOVA-test for the normally distributed variables and Kruskal-Wallis test for the non-normally distributed variables.

The paired t-test and Wilcoxon signed-rank test were used to assess training induced changes (pre vs. post) within a particular group. The effect of intervention among the groups, the effect of time and the effect of group-by-time interactions were evaluated using repeated measures analysis of variance (RMANOVA).

Friedman test was used when data was not normally distributed, knowing that normality was tested using Kolmogorov-Smirnov test.

The inflation of type-I error due to multiple comparisons was controlled using Bonferroni rule. Statistical analyses were performed using SPSS software (version 20, SPSS Inc., Chicago, Illinois, U.S.A.).

III. RESULTS

A total of 53 patients were assessed for eligibility and 20 patients were recruited. After the first office meeting, 25 patients failed to reach randomization and eight others did not participate for the following reasons: long distance, family issues and other limitations.

No side effects have been recognized during the training period, and all patients in training groups seemed to be enthusiastic and interested. Compliance was monitored using a daily log booklet, and was excellent in the two groups.

Drugs were taken properly by all the patients according to their cardiac specialist instructions (ACE- or ARB, beta blockers, and diuretics).

Pharmacological therapy has not been changed over the 3-month training period. At baseline, there were no statistically significant differences among the two groups (Control and RT) with respect to demographic characteristics, drugs, Cardiac Function, Exercise Test, Pulmonary Function Test, Functional capacity, Qol Respiratory muscle function and leg skeletal muscle function (Table I).

Table I: Demographic and clinical characteristics of patient population

	Control	RT	P-value
Ages	52.6±11.2	55±6.7	0.440*
Females/Males	4/4	3/5	0.600*
BMI	31.3±3.4	33.3±4.9	0.514
Medication (%)			
ARB	10	50	0.254
B-blockers	33.3	33.3	0.994
Diuretics	38.1	28.6	0.773
ACE-I	36.4	31.8	0.899
EF (%)	36.1±8.2	36.6±2.6	0.729
LVEDD (mm)	58.3±6.6	64.6±5.2	0.069
LVESD (mm)	46±5.9	52±8.1	0.454*
LVEDV (ml)	130±38.9	135.9±38.6	0.797*
LVESV (ml)	93.3±30.3	98.8±30.3	0.781
Exercise time	475.5±144.7	421.5±124.4	0.532
METs	8.1±2.1	8.3±1.9	0.337*
MLWHF_score	29.9±10.6	34.1±13.6	0.968*
FVC	3.2±0.8	2.9±0.8	0.873*
FEV1	2.4±0.9	2.5±0.7	0.912
FEV1/FVC	74.9±11.7	86.6±11.6	0.090
6MWT (meters)	455.3±113.1	425.7±62.9	0.539
MEP (mmHg)	70.1±16.7	89.6±29.5	0.094
MIP (mmHg)	35.8±10.5	44.3±7.5	0.151
SPImax (seconds)	176±89.7	168.1±80.9	0.913
MVIF right (Kg)	18.0±4.7	19.7±4.1	0.578
Maintenance right (seconds)	105.0±30.3	90.6±24.9	0.536
Stage	2.8±0.9	2.6±0.9	0.921*
MVIF left (Kg)	18.1±3.7	21.2±2.6	0.152
Maintenance left (sec)	118±43.3	89.6±40.1	0.210
NYHA class	2±0.8	2.1±0.6	0.921*
Dyspnea	12.8±2.3	12.3±1.0	0.598*

Compared to control, the training group had 18% ($p<0.05$) and 11% ($p<0.05$) improvement in the right and left MVIF respectively, and a 24% improvement in the right quadriceps muscle endurance capacity (MT) ($p<0.05$).

Moreover, RT has shown a 27% improvement in exercise time ($p<0.01$), 24% in METS ($p<0.01$), and a 15% improvement in dyspnea sensation ($p<0.001$) (Figure 4). A significant increase in 6MWT distance (13%, $p<0.01$), a decrease in NYHA functional class (33%, $p<0.05$), and a decrease in MLWHFQ score (30%, $p<0.05$) were also noticed in figure 3. In addition, a little increase in (LVEF) was observed in RT (5%, $p<0.05$) versus no changes in the control group (Figure 2). Concerning respiratory muscle function, RT was able to improve MIP by 14% ($p<0.01$).

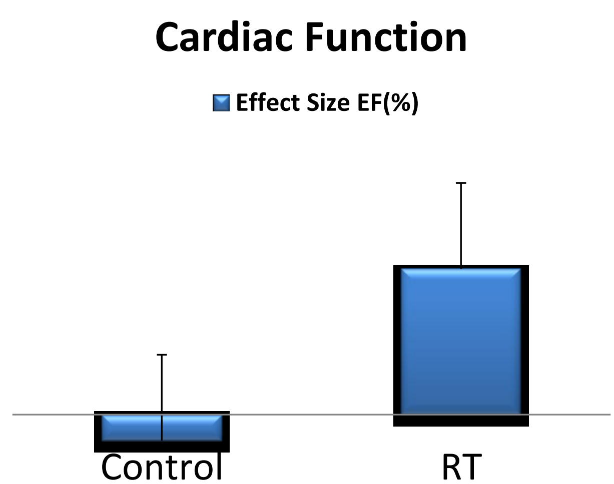

Figure 2. Effect size in cardiac function. Control: NS improvement in the cardiac function. RT: Significant improvements in EF (P<0.01). RT, Resistance Training; EF: Ejection Fraction.

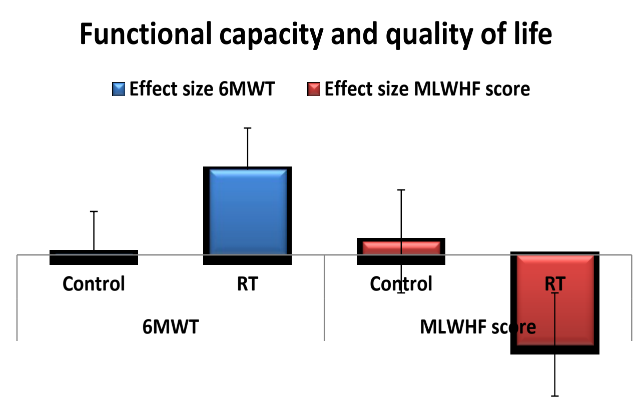

Figure 3. Effect size in Functional capacity (6MWT) and Quality of life (MLWHF). Control: No significant improvement in functional capacity and quality of life. RT: Significant improvements in 6MWT (13%, P=0.01), MLwHF score (30%, P=0.05).

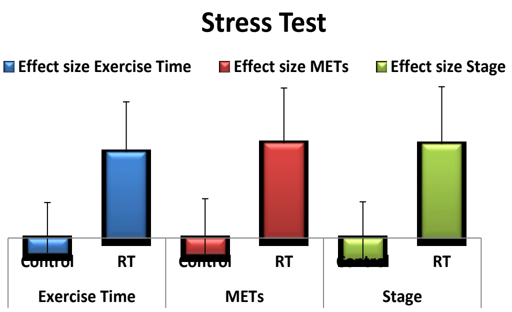

Figure 4. Effect size in Stress test. Control: No significant improvement in Mets (Metabolic Equivalent) and exercise time. RT: Significant improvements in Mets (24%, P=0.008), exercise time (27%, P=0.01).

IV. Discussion

In this study, RT was able to bring out significant improvements in the skeletal muscle function, the cardiac function, NYHA functional class, and dyspnea as well as on functional capacity and QoL. Surprisingly, RT has also shown significant impact on respiratory muscle strength. Since the control group had no significant improvements in any of these parameters, we can confirm the effectiveness of the RT.

The benefits gained in skeletal muscle function affect positively the overall exercise performance and are closely related to beneficial adaptations in the muscle structure and function such as an increase in type 1 fiber, decrease in circulatory pro-inflammatory markers and a better muscle oxidative capacity [8]. In addition, such an intensive RT might induce an increase in the motor unit recruitment and so will impact on root mean square (RMS) value towards an upward trend.

In addition, we observed that the right quadriceps muscle is stronger than the left quadriceps muscle. These variations can be explained by the fact that maybe most of patients are right leg dominants.

Besides, as known, skeletal and respiratory muscle changes in heart failure are associated with biochemical and metabolic disorders. Thus, the fact of improvement in respiratory muscle function in our study may be attributed to the beneficial effects of RT in increasing mitochondrial enzymes and decreasing pro-inflammatory cytokines [4].

The skeletal muscle hypothesis confirms that impairments in the skeletal muscle not only alter the skeletal muscle by itself, but also contribute to further deteriorations and worsens the symptoms [21]. In the same manner as this hypothesis, RT also works not only by improving the skeletal muscle function, but also by enhancing the overall exercise performance and QoL, thus reducing hospitalizations as well as mortality rates. Therefore, regular RT programs are very efficient in counteracting these negative skeletal muscle abnormalities seen in CHF.

V. Conclusion

Considering our findings, we highly recommend the use of resistance training in CHF and IMW patients. This study had shown the crucial effect of RT, for it has improved the respiratory muscle strength. RT was safe and effective in improving skeletal muscle function, exercise performance, dyspnea and QoL in CHF patients, as well as in improving cardiac LVEF. Surprisingly in our study, RT improved respiratory muscle function in addition to improving cardiac left ventricular EF%.

We recommend that future studies investigate the usefulness of the electrical activity of the muscles known as Electromyography (EMG) in clinical diagnosis, in heart failure patients, in order to monitor the progression of skeletal muscle activity and function. Cardiac biomarkers could also be assessed in order to confirm the safety and effectiveness of interventions. Furthermore, studies at the cellular level could be a plus if added to the non-invasive measurements we used. Finally, biopsies of skeletal muscle might give a clearer insight about potential skeletal muscle adaptations after exercise conditioning.

It was not possible to assess aerobic capacity through measuring peak oxygen consumption (VO2max). However, we have used 6MWT and METs as prognostic outcomes. Both METs and 6MWT have been approved to be used instead of direct measurement of oxygen uptake [22], [23]. In addition, there is heterogeneity in training load, especially in exercise duration.

Acknowledgment

This research was supported by a fund from the National Council for Scientific Research (CNRS), Beirut, Lebanon; and was approved by the ethics committee of Beirut Cardiac Institute, Beirut, Lebanon.

References

[1] Z. Sadek, S. Ahmaidi, M. Youness, W. Joumaa, C. Awada, and W. Ramadan, "Impact of Resistance Training in Patients with Chronic Heart Failure," The Seventh International Conference on Global Health Challenges, Athens, Greece, pp. 44–46, 2018.

[2] M. Grazzini, L. Stendardi, F. Gigliotti, and G. Scano, "Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD)," *Respir. Med.*, vol. 99, no. 11, pp. 1403–1412, 2005.

[3] M. F. Piepoli and A. J. S. Coats, "The 'skeletal muscle hypothesis in heart failure' revised," *Eur. Heart J.*, vol. 34, no. 7, pp. 486–488, 2013.

[4] C. Zizola and Schulze P. Christian, "Metabolic and structural impairment of skeletal muscle in heart failure," vol. 6, no. 5, pp. 247–253, 2009.

[5] M. J. Sullivan, H. J. Green, and F. R. Cobb, "Altered skeletal muscle metabolic response to exercise in chronic heart failure. Relation to skeletal muscle aerobic enzyme activity," *Circulation*, vol. 84, no. 4, pp. 1597–1607, 1991.

[6] M. Schaufelberger, B. O. Eriksson, G. Grimby, P. Held, and K. Swedberg, "Skeletal muscle fiber composition and capillarization in patients with chronic heart failure: relation to exercise capacity and central hemodynamics," *J. Card. Fail.*, vol. 1, no. 4, pp. 267–72, 1995.

[7] H. Drexler, U. Riede, T. Munzel, H. Konig, E. Funke, and H. Just, "Alterations of skeletal muscle in chronic heart failure," *Circulation*, vol. 85, pp. 1751–1759, 1992.

[8] C. Delagardelle, P. Feiereisen, P. Autier, R. Shita, R. Krecke, and J. Beissel, "Strength/endurance training versus endurance training in congestive heart failure," *Med Sci Sport. Exerc*, vol. 34, no. 12, pp. 1868–1872, 2002.

[9] C. D. Mcdonald, G. E. Burch, and J. J. Walsh, "Prolonged Bed Rest in the Treatment of the Dilated Heart," *Circulation*, vol. 32, no. 5, pp. 852–856, 1965.

[10] S. M. Robert, Lm. Nei, T. Charles, B. Robert, and M. J.Duncan, "Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy," *Am. J. Cardiol.*, vol. 76, no. 12, pp. 977–979, 1995.

[11] K. Meyer, K. Hajric, R.Westbrook, S. Haag Wildi, S. Holtkamp, R. Leyk, D. Schnellbacher, "Hemodynamic responses during leg press exercise in patients with chronic congestive heart failure," *Am. J. Cardiol.*, vol. 83, no. 11, pp. 1537–1543, 1999.

[12] T. Grosse, K. Kreulich, H. Naegele, "Peripheral muscular strength training in patients with severe heart failure," *Dtsch Z Sport.*, vol. 52, pp. 11–14, 2001.

[13] C. T. Pu, M T. Johnson, D E. Forman, J M. Hausdorff, R. Roubenoff, M. Foldvari, R A. Fielding, M A. Singh, "Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure," *J Appl Physiol*, vol. 90, no. 6, pp. 2341–2350, 2001.

[14] I. Levinger, R. Bronks, D. V. Cody, I. Linton, and A. Davie, "Resistance training for chronic heart failure patients on beta blocker medications," *Int. J. Cardiol.*, vol. 102, no. 3, pp. 493–499, 2005.

[15] I. Levinger, R. Bronks, D. V Cody, I. Linton, and A. Davie, "Perceived exertion as an exercise intensity indicator in chronic heart failure patients on Beta-blockers," *J. Sports Sci. Med.*, vol. 3, no. YISI 1, pp. 23–7, 2004.

[16] G. Magnusson, A. Gordon, L. Kaijser, C. Sylven, B. Isberg, J. Karpakka, B. Saltin, "High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement," *Eur Hear. J*, vol. 17, no. 7, pp. 1048–1055, 1996.

[17] P. Ponikowski, A.Voors, S. Anker, H. Bueno, J. Cleland, A. Coats, F. Andrew, G. Volkmar, R. José, V. Harjola, E.Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J. Parissis, B. Pieske, J. Riley, G. Rosano, L. Ruilope, F. Ruschitzka, F. Rutten, P. Van Der Meer, "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure," *Eur. Heart J.*, vol. 37, no. 27, p. 2129–2200m, 2016.

[18] C. L. Craig Craig, A. Marshall, M. Sjöström, A. Bauman, M. Booth, B. Ainsworth, M. Pratt, U. Ekelund, A. Yngve, J. Sallis, P. Oja, "International physical activity questionnaire: 12-Country reliability and validity," *Med. Sci. Sports Exerc.*, vol. 35, no. 8, pp. 1381–1395, 2003.

[19] A. L. Beatty, N. B. Schiller, and M. A. Whooley, "Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the Heart and Soul Study," *Arch Intern Med*, vol. 172, no. 14, pp. 1096–1102, 2012.

[20] S. Grant, T. Aitchison, E. Henderson, J. Christie, S. Zare, J. McMurray, H. Dargie,"A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and likert scales in normal subjects during submaximal exercise," *Chest*, vol. 116, no. 5, pp. 1208–1217, 1999.

[21] T. S. Rector and J. N. Cohn, "Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan," *Am. Heart J.*, vol. 124, no. 4, pp. 1017–1025, 1992.

[22] A. L. Clark, P. A. Poole-Wilson, and A. J. S. Coats, "Exercise limitation in chronic heart failure: Central role of the periphery," *J. Am. Coll. Cardiol.*, vol. 28, no. 5, pp. 1092–1102, 1996.

[23] J. R. Wicks, N. B. Oldridge, L. K. Nielsen, and C. E. Vickers, "HR Index—A Simple Method for the Prediction of Oxygen Uptake," *Med. Sci. Sports Exerc.*, pp. 2005–2012, 2011.

[24] S. Miyamoto**,** N. Nagaya, T. Satoh, K. S. Kyotani, F. Sakamaki, M. Fujita, N. Nakanishi, K. Miyatak, "Clinical Correlates and Prognostic Significance of Six-minute Walk Test in Patients with Primary Pulmonary Hypertension," *Am. J. Respir. Crit. Care Med.*, no. 3, 2012.