EFFECT OF INSPIRATORY MUSCLE TRAINING ON CARDIAC PARAMETERS OF EXERCISE TOLERANCE TEST IN CHRONIC HEART FAILURE PATIENTS

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Abstract

Introduction: inspiratory muscle training (IMT) improves exercise capacity and ventilatory responses to exercise in chronic heart failure (CHF) patients with inspiratory muscle weakness (IMW). **Aim of work:** To investigate the effect of inspiratory muscle training (IMT) with comprehensive cardiac rehabilitation (CR) program (aerobic and resisted exercise training) on cardiac parameters of exercise tolerance test in chronic heart failure patients **Materials and Methods:** Forty eligible male patients with chronic heart failure secondary to ischemic heart disease (only thirty of them completed the study). Their ages ranged from 50-60 years old .They were randomly assigned to 6 months of aerobic exercise , resisted exercise plus IMT (n=15) or to aerobic exercise plus resisted exercise only (n=15), before and after intervention, the following measures were obtained :cardiac parameter of cardiopulmonary exercise testing (maximum heart rate , resting heart rate). **Result:** Compared aerobic exercise (AE) + IMT to AE resulted in cardiac parameters of exercise tolerance test (maximum heart rate, resting heart rate) improved similarly in the 2 groups. **Conclusion:** This study demonstrated that the addition of IMT to AE results in improvement in cardiac response to exercise in selected patients with CHF but with no significant difference between exercise training groups.

Keyword: Inspiratory muscle training, Chronic heart failure, Cardiac parameters of exercise tolerance test, and Aerobic exercise.

Introduction

Chronic heart failure (CHF) is a major public health problem causing considerable morbidity, mortality and economic burden (Vizzardi et al .,2009) it is appears to result not only from cardiac overload or injury but also from a complex interplay among genetic, neurohormonal, inflammatory, and biochemical changes acting on cardiac myocytes, the cardiac interstitium, or both . (Braunwald, 2008)

HF can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures) (McMurray et al ., 2012) .

The major symptoms of CHF include exertional dyspnea, fatigue, exercise intolerance, and functional limitations. Each of the 3 systems participating in the exercise intolerance; the central circulation, the peripheral vessels and skeletal muscles, and the ventilatory system (Balady, 2003).

Inspiratory muscle weakness, which occurs in 30% to 50% of the heart failure patients, is associated with reduction in the functional capacity, reduction in the quality of life (Qol) and with a poor prognosis in these individuals. (Derchak et al .,2002) and (Sheel et al .,2002) have shown that inspiratory muscles can also limit physical performance to exercise in healthy subjects and also in athletes. Similarly, changes in the inspiratory muscles play an important role in the pathophysiology of exercise limitation in HF. One of these changes is the inspiratory muscle weakness, arbitrarily defined as a maximal inspiratory pressure (PImax) less than 70% of the predicted for age and sex. Patient with inspiratory muscle weakness may have a reduced functional capacity determined by the peak oxygen consumption (VO2 peak). In addition, inspiratory muscle strength and resistance are directly associated to VO2 peak in patients with recent acute myocardial infaction18, reinforcing the idea that the inspiratory muscles may contribute for the reduction of functional capacity (Ribeiro et al., 2012).

Reduced capacity to perform aerobic exercise is a hallmark of CHF and seems to be under influence of several factors, especially reduced blood flow to skeletal muscles during exercise due to impairment in cardiac output and other aforementioned abnormalities. CHF patients may achieve less than half of the maximal attainable cardiac output at peak exercise level. Patients with CHF have an already reduced stroke volume that only rises modestly up to 50 to 65 percent of the stroke volume (SV) of the healthy subjects during exercise. A reduced SV along with a lower maximal achievable heart rate at peak exercise in these patients are the main factors behind a reduced cardiac output. Impaired left ventricular (LV) systolic function and a reduced preload reserve decrease the ability of the already dilated LV to increase End Diastolic Volume (EDV). In addition, a decreased chronotropic reserve reduces the degree of increase in heart rate above the resting level, because of an already elevated heart rate at rest and lower attainable maximum heart rate at peak exercise level. The reduction in heart rate immediately after exercise (heart rate recovery), which is considered to be an indicator of parasympathetic nervous system tone, is also reduced in CHF patients (Movahed et al., 2013).

Inspiratory muscles training (IMT) is a technique that is designed to improve the performance of the respiratory muscles (RM) that may be impaired in a variety of conditions. Interest in IMT has expanded over the past two decades, and it has been used in an increasingly wide range of clinical conditions (Bott et al .,2009).

Selective inspiratory muscle training is effective in patients with chronic heart failure .Mechanisms underlying these beneficial effects of IMT included attenuated metaboreflex, improved ventilatory efficiency, and lower ventilatory oscillations during incremental exercise. It is proposed that the metabolic products accumulated from fatiguing respiratory muscle contraction could increase sympathetic vasoconstriction activity (the inspiratory muscle metaboreflex), and the attenuation of the metaboreflex could then improve blood flow redistribution to skeletal muscles in the body, thereby delaying the time to fatigue and decreasing workload on the heart (Wong et al .,2011)

Aim of work: To investigate the effect of inspiratory muscle training (IMT) with comprehensive cardiac rehabilitation program (aerobic and resisted exercise training) on cardiac parameters of exercise tolerance test (maximum heart rate, resting heart rate) in chronic heart failure patients.

Materials and Methods

Study design: it is cross sectional study

Place and duration of the study: the study was carried in national heart institute. During the period from March 2013 till July 2014.

Study sample: Forty eligible male patients with chronic heart failure secondary to ischemic heart disease but only thirty of them completed the study. They were diagnosed by echocardiography and coronary angiography. Their ages ranged from 50-60 years old .The patients had been clinically and medically stable for more than three months prior to the onset of study period.

Inclusion criteria was:- The diagnosis of ischemic cardiomypathy , they were on optimal medical therapy with no major changes in treatment regimen during the study , left ventricular end-diastolic dimension > 5.5cm and end-systolic diameter > 4.5cm, Fractional shortening < 25% and ejection fraction < 40%. , New York Heart Association (NYHA) class II-III.

Study methods : They was randomly divided into two groups equal in number and age matched, similarity of both groups should be accurate with respect to age, weight, height and body mass index (BMI). All participants were informed about the nature and effects of trial. They have been given an informed written consent form.

Group (A) (Training group): Fifteen patients participated in a supervised comprehensive cardiac rehabilitation program which is composed of: Aerobic training: in form of Interval aerobic training: Strengthening exercise, Resistance/ strength training and Inspiratory muscle trainer. The training subjects received information as regard the benefits of regular aerobic exercise and were asked to report any side effects during the treatment session.

Group (B): (Control group): Fifteen patients participated in comprehensive aerobic training: in form of Interval aerobic training and Strengthening exercise: Resistance/ strength training.

II. Instrumentation:

1. **For assessment:** Oxycon pro (ER-900, Ergoline, Jaeger, Würzburg, Germany) cardiopulmonary exercise test unit with 12 channel ECG, gas analyzer to measure maximal O_2 uptake and anaerobic threshold , Mercurial sphygmomanometer is used to for measuring blood pressure before, during, and after exercise training sessions, Free weights for assessing maximum voluntary contraction by one repetition maximum test before conducting the circuit weight training for both groups , Maximum Inspiratory Pressure meter (care fusion UK 2321td) to determine the inspiratory muscle strength before and after training in both groups.
2. **For training:** Inspiratory muscle trainer: (Threshold inspiratory muscle trainer; Respironics(Cedar Grove, New Jersey 07009-1201 USA), used for training the study group. The device contains a spring-loaded valve, attached to a mouthpiece through which subjects inspire while wearing a nose clip. The valve controls a constant inspiratory pressure training load and the patient must generate the inspiratory pressure in order for the inspiratory valve to be opened and allow inhalation of air. The amount of resistance can be adjusted by varying the compression of the spring-loaded valve. Adjustment from $7cmH_2O$ to $41cmH_2O$ is possible (Crowe et al., 2008).

III. Procedure:

Evaluation procedure:

II- Cardiopulmonary exercise testing (CPET):

The equipment consists of a metabolic cart and a static cycle/ treadmill. The metabolic cart contains gas analyser, a computer and screens which display continuously 12-lead ECG ST segment analysis and graphical displays of the physiological changes as they occur during exercise. The gas analyzers are capable of breath-by breath measurement of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) and flow calibration is done before each test. The test is performed in an adequately ventilated room with all resuscitation facilities. (Agnew, 2010).

After a period of rest to allow the patient to become familiar with the equipment and the bicycle, the resting Heart Rate (HR), Blood Pressure (BP), SpO_2, ECG and gas exchange values are recorded. In a cycle ergometer the saddle height is adjusted and patients advised to pedal at constant speed of 50 to 60 rpm with monitors attached and the tight-fitting face mask in place seal over the patients' nose and mouth to prevent air leakage, with no resistance for a short period of 2 to 3 minutes. Then work rate is increased by 10 to 20 W. min-1 by the computer, increasing the resistance of the pedals (bicycle) while the subject maintains a constant pedaling rate (bicycle). All patients were subjected to a submaximal exercise testing on stationary ergometry of the cardiopulmonary exercise test before and after training programs according to Ramp protocol. The optimal duration of the test is around ten minutes for proper assumption of the VO_2max . The maximum aerobic capacity i.e. VO_2max is the highest VO_2 recorded when a patient's VO_2 value reaches a plateau with work rate increments and are based on predetermined formulae using the patients age, height, gender and weight exercise finishes with a cool down stage in which the patient pedals the bicycle for a brief period against zero resistance (Chatterjee et al., 2013).

Training procedure:

Both groups of patients performed a supervised individual training program based on the result of cardiopulmonary exercise testing. Both groups were trained using heart rate range or reserve method (Karvonen's method); training heart rate (THR=HR_{rest} + (HR_{max} – HR_{rest}) 55-85% This formula is the most accurate one (Kennedy et al .,2012)

- Mode of exercise: treadmill and cycle ergometer.

- Intensity of exercise: the patient should not exceed his training heart rate during exercise period. The training heart rate increased gradually according to each patient's response during exercise training session, starting with 55% of heart rate reserve, till trying to reach 85% at the end of 6th month.

-Type of exercise: The conditioning phase of each session involved aerobic training (cycle ergometer, treadmill walking) and resistance/strength training.

Aerobic training: at the prescribed heart rate intensity. All subjects used a heart rate monitor (Telemetry, Hewlett Packard (HP) M2604A) to obtain the assigned exercise intensity. The Borg 6-to-20 scale used to assess the rate of perceived exertion during and after each training session. Patients in both groups exercised continuously for 45 minutes without breathing heavily, the progression of exercise training appeared as the number of bouts along 45 min of exercise training decrease gradually until it can reach at end of 6 months to no rest with one bout of training.

Resistance/strength training (RST): Consists of eight resistance exercises for different eight large muscle groups (shoulder flexors and extensors, elbow flexors and extensors, hip flexors and extensors and knee flexors and extensors). It was applied for both groups of patients.

RST can be started with a high number of repetitions (12–25) and a low intensity (30–40% 1-RM). When the patient is confident with the exercise, he can proceed to the next phase.

As RST at higher intensity become (40–60% 1-RM) in order to increase muscle mass after 2 months. Repetitions were slowly increased from 1 _ 10, 1 _ 15, 2 _ 10 to 2 _ 15. Between each series of repetitions 1 min rest was allowed. Patients were instructed in correct lifting techniques, to avoid Valsalva manoeuvre . So intensity will be detected initially, by increasing the number of exercise circuits from one to three, followed by increasing the resistance or cycling load (Piepoli et al., 2011).

-Duration: each exercise session included three phases:

Warm up phase: an initial 5-10 minutes in the form pedaling on bicycle ergometer, walking on treadmill or active stretching exercises with breathing. The heart rate during warm-up phase reached 30-40% of the target heart rate.

Aerobic phase: at the prescribed heart rate intensity. This phase started in short bouts about 8 minutes for 24 minutes, gradually prolonged up till continuous 45 minutes at the end of the 7^{th} months.

Cool down phase: for 5-10 minutes with intensity decreased gradually to resting heart rate.

Frequency: exercise training done three times per week for six months.

Patients in group A (study group) performed the breathing exercise with the inspiratory muscle trainer for 7 sets with an inspiratory load at 30% of PImax, three time per week for six months ; training loads were adjusted to maintain 30% of the PImax (Winkelmann et al, 2009).

The patients were taught the following instructions for proper inspiratory muscle training:

- Sit in a comfortable position and put the nose clip on the nose, inhale through the mouth only.
- Relax, place the lips around the mouthpiece, and inhale as deeply as you can with enough force to open the valve.
- Exhale through the mouthpiece; continue inhaling and exhaling without removing the device from the mouth.
- Repeat inhaling 7 sets every set 3 minutes with enough resting period's in-between sets (1min). Total time of training 28 minutes three time per week.

Data management:

- Descriptive statistics and t-test for comparison of the mean age, weight, height, BMI and duration of infarction, EF, FS between both groups (study and control).
- Mixed ANOVA was conducted to compare the effect of time (pre versus post) and the effect of treatment (between groups), as well as the interaction between time and treatment on mean values of measured variables.
- The level of significance for all statistical tests was set at $p < 0.05$.
- All statistical measures were performed through the statistical package for social studies (SPSS) version 19 for windows.

Consent:

Authors declare that verbal consent was taken from the studied group before making the study.

Ethical approval:

The ethical committee of faculty of physical therapy approved the study protocol.

Results

Comparing the subject demographic and clinical characteristics data of both groups revealed that there was no significance difference between both groups ($p > 0.05$).

Comparison of cardiac parameters of cardiopulmonary exercise testing between both groups:

Table 1: Mean values of Max HR pre and post treatment of group A and group B:

Max HR (beat/min)				
Study group		**Control group**		
$\overline{X} \pm SD$		$\overline{X} \pm SD$		
Pre treatment	**Post treatment**	**Pre treatment**		**Post treatment**
120.9 ± 8.99	113 ± 8.29	121.7 ± 7.68		115.6 ± 8.5
Within group comparison				
		MD	**% of improvement**	**p-value**
Pre test vs. post test	Study group	7.9	↓ 6.53	0.0001*
	Control group	6.1	↓ 5.01	0.0001*
Between group comparison				
		MD	**p-value**	
Study vs control	Pre	-0.8	0.83	
	Post	-2.6	0.49	

$\overline{X}$: Mean SD: Standard Deviation MD: Mean difference

p value: Probability value *: Significant

Table (1) showed that there was no significant difference in the mean values of Max HR post treatment between group A and group B ($p = 0.49$).

Table 2: Mean values of RHR pre and post treatment of study and control groups:

Resting HR (beat/min)				
Study group		**Control group**		
$\overline{X} \pm SD$		$\overline{X} \pm SD$		
Pre treatment	Post treatment	**Pre treatment**		**Post treatment**
77.3 ± 10.78	70.9 ± 9.68	72 ± 7.93		68.1 ± 7.69
Within group comparison				
		MD	**% of improvement**	**p-value**
Pre test vs. post test	Study group	6.4	↓ 8.27	0.0001*
	Control group	3.9	↓ 5.41	0.0001*
Between group comparison				
		MD	**p-value**	
Study vs control	Pre	5.3	0.22	
	Post	2.8	0.48	

$\overline{X}$: Mean SD: Standard Deviation MD: Mean difference
p value: Probability value *: Significant

Table (2) showed that there was no significant difference in the mean values of resting heart rate (RHR) post treatment between study and control groups (p = 0.48).

Discussion

With regard to the comparison between the two groups the results of the present study revealed no significant difference between both groups in measuring cardiac parameter of exercise tolerance test (maximum heart rate and resting heart rate).

Jaenisch et al .,2011 agreed with our study as he evaluate the effects of RMT on the hemodynamic and autonomic function, arterial baroreflex sensitivity (BRS), and respiratory mechanics in rats with heart failure (HF) . Rats were assigned to one of four groups: sedentary sham (*n* _ 8), trained sham (*n* _ 8), sedentary HF (*n* _ 8), or trained HF (*n* _ 8). Trained animals underwent a RMT protocol (30 min/day, 5 day/wk, 6 wk of breathing through a resistor), whereas sedentary animals did not. In HF rats, RMT had significant effects on several parameters. It reduced left ventricular (LV) end-diastolic pressure (*P* _ 0.01), increased LV systolic pressure (*P* _ 0.01), and reduced right ventricular hypertrophy (*P* _ 0.01) and pulmonary (*P* _ 0.001) and hepatic (*P* _ 0.001) congestion. It also decreased resting heart rate (HR; *P* _ 0.05), indicating a decrease in the sympathetic and an increase in the vagal modulation of HR. There was also an increase in baroreflex gain (*P* _ 0.05). These findings show that a 6-wk RMT protocol in HF rats promotes an improvement in hemodynamic function, sympathetic and vagal heart modulation, arterial BRS, and respiratory mechanics, all of which are benefits associated with improvements in cardiopulmonary interaction.

Witt et al., 2007 hypothesized that inspiratory muscle training (IMT) would attenuate the sympathetically mediated heart rate (HR) and mean arterial pressure (MAP) increases normally observed during fatiguing inspiratory muscle work. An experimental group (Exp, *n*=8) performed IMT 6 days per week for 5 weeks at 50%of maximal inspiratory pressure (MIP), while a control group (Sham, *n*=8) performed IMT at 10% MIP. Pre- and post-training, subjects underwent a eucapnic resistive breathing task (RBT) (breathing frequency=15 breaths min−1, duty cycle=0.70) while heart rate (HR) and mean arterial pressure (MAP) were continuously monitored. Following

IMT, MIP increased significantly ($P < 0.05$) in the Exp group (−125±10 to −146±12 cmH2O; mean± S.E.M.) but not in the Sham group (−141±11 to −148±11 cmH2O). Prior to IMT, the RBT resulted in significant increases in HR (Sham: 59±2 to 83±4 beats min−1; Exp: 62±3 to 83±4 beats min−1) and MAP (Sham: 88±2 to 106±3 mmHg; Exp: 84±1 to 99±3 mmHg) in both groups relative to rest. Following IMT, the Sham group observed similar HR and MAP responses to the RBT while the Exp group failed to increase HR and MAP to the same extent as before (HR: 59±3 to 74±2 beats min−1; MAP: 84±1 to 89±2 mmHg). This attenuated cardiovascular response suggests a blunted sympatho-excitation to resistive inspiratory work. So reducing activity of chemosensitive afferents within the inspiratory muscles and may provide a mechanism for some of the whole-body exercise endurance improvements associated with IMT.

On the other hand Beckers et al ., 2008 compare the effects of combined endurance-resistance training (CT) with endurance training (ET) only on submaximal and maximal exercise capacity, ventilatory prognostic parameters, safety issues, and quality of life in patients with chronic heart failure (CHF) .Fifty-eight CHF patients New York Heart Association (NYHA class II–III) were randomized either to 6 months CT [n ¼ 28, 58 years, left ventricular ejection fraction (LVEF) 26%, VO2peak 18.1 mL/kg/min] or ET (n ¼ 30, 59 years, LVEF 23%, VO2peak 21.3 mL/ kg/min). The increase in steady-state workload (P ¼ 0.007) and the decrease in heart rate at SSW (P ¼ 0.002) were significantly larger in CT-compared with ET-trained patients.

Also an aerobic training program in patients with CHF regularly reduces the resting heart rate, which indicates a reduction in sympatho-adrenergic drive.

Conclusion

This study demonstrates that reducing activity of chemosensitive afferents within the inspiratory muscles may provide a mechanism for some of the whole-body exercise endurance improvements associated with IMT.

Conflict of interest

Authors have declared that no conflict of interests exists.

References

1. Agnew N (2010): Preoperative cardiopulmonary exercise testing. Continuing Education in Anesthesia. Critical Care and Pain; 10: 33-37.
2. Balady G J (2003): Exercise intolerance and the role of exercise training in heart failure, Cardiology Rounds; 7 (5):1-6.
3. Beckers P J, Denollet J, Possemiers NM, Wuyts FL, Vrints CJ, and Conraads V M (2008) : Combined endurance-resistance training vs. endurance training in patients with chronic heart failure: a prospective randomized study . European Heart Journal; 29:1858–1866.
4. Bott J, Blumenthal S, Buxton M, Ellum S, Falconer C, Garrod R, Harvey A, Hughes T, Lincoln M, Mikelsons C, Potter C, Pryor J, Rimington L, Sinfield F, Thompson C, Vaughn P and White J (2009): Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Thorax ; 64 (1):1–51
5. Braunwald E (2008): Biomarkers in Heart Failure. N Engl J Med ;358 :2148-2159
6. Chatterjee1 S, Sengupta S, Nag M, Kumar P, Goswami1 S and Rudra A (2013): Cardiopulmonary Exercise Testing: A Review of Techniques and Applications .J Anesth Clinic Res; 4:7.
7. Crowe J and Bradley C (2008): The effectiveness of incentive spirometry with physical therapy for high risk patients after coronary artery bypass surgery. Phys Tnco; 17:260-268.
8. Derchak PA, Sheel AW, Morgan BJ, Dempsey JA (2002): Effects of expiratory muscle work on muscle sympathetic nerve activity. J Appl Physiol; 92(4):1539-52.
9. Jaenisch RB, Hentschke VS, Quagliotto E, Cavinato PR, Schmeing LA, Xavier LL and Dal Lago P (2011): Respiratory muscle training improves hemodynamics, autonomic function, baroreceptor sensitivity, and respiratory mechanics in rats with heart failure .J Appl Physiol; 111: 1664–1670.
10. Kennedy K, Adams J, Cheng D, and Berbarie Ra F (2012): High-intensity track and field training in a cardiac rehabilitation program: Proc (Bayl Univ Med Cent); 25(1):34–36
11. McMurray JV, Adamopoulos S, Anker SD, Auricchio A , Bo¨hm M , Dickstein K , Falk V, Filippatos G , Fonseca C , Gomez-Sanchez M A , Jaarsma T , Køber L , Lip YH , Maggioni A P , Parkhomenko A , Pieske BM, Popescu BA , Rønnevik PK, Rutten FH, Schwitter J , Seferovic P , Stepinska J , Trindade PT , Voors AA , Zannad F and Zeiher A (2012) : ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012.The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. European Heart Journal; 33: 1787–1847.
12. Movahed H, Cao L B, Pitzalis M and Movahed A (2013): Beneficial Effects of Exercise Training in Patients with Chronic Heart Failure .Journal of Cardiology and Therapeutics; 1(1):20-33.
13. Piepoli M F , Conraads V, Corra U , Dickstein K , Francis D P, Jaarsma T , McMurray J , Pieske B , Piotrowicz E , Schmid J-P , Anker SD, Solal1 AC , Filippatos GS , Hoes AW , Gielen S , Giannuzzi P and Ponikowski PP (2011): Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular. Prevention and Rehabilitation European Journal of Heart Failure; 13: 347–357.
14. Ribeiro JP, Chiappa GR and Callegaro CC: The contribution of inspiratory muscles function to exercise limitation in heart failure: pathophysiological mechanisms .Rev Bras Fisioter; 16(4):261-267.
15. Sheel AW, Derchak PA, Pegelow DF A and Dempsey JA (2002): Threshold effects of respiratory muscle work on limb vascular resistance. Am J Physiol Heart Circ Physiol; 282(5):732-8.

16. Vizzardi E , Bonadei I, Zanini G, Frattini S, Fiorina C, Raddino R and Dei Cas L (2009): Homocysteine and Heart Failure: An Overview Recent Patents on Cardiovascular Drug Discovery; 4 (1) : 15-21 .
17. Winkelmann ER, Chiappa GR, Lima CO, Viecili PR, Stein R, Ribeiro JP (2009): Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. Am Heart J;158 (5):768.e1-768.e7.
18. Witt J D, Guenette J A, Rupert J L, McKenzie D C and Shee AW (2007): Inspiratory muscle training attenuates the human respiratory muscle metaboreflex. J Physiol; 584(3):1019–1028.
19. Wong E, Selig S and Hare DL (2011): Respiratory muscle dysfunction and training in chronic heart failure. Heart Lung Circ; 20(5):289-294.