# Cardiac Rehabilitation in Patients with Heart Failure

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Reduced exercise capacity negatively affects the ability of patients with heart failure (HF) to perform activities required for daily life, further decreasing their independence and quality of life (QoL). Cardiac rehabilitation (CR) can effectively improve aerobic fitness and overall health status in patients with HF. Low referral rate is an important limitation that may impede successful CR, whereas the automatic referral and liaison strategies performed by some healthcare providers manifestly increase the CR referral rate. However, there is still controversy regarding the most effective exercise strategy for improving hemodynamic efficiency during daily activities in the HF population. Aerobic interval training (AIT), that includes alternating high- and low-intensity exercise sessions, may be a more effective modality for improving functional capacity than traditional moderate continuous training (MCT) in patients with HF. A novel AIT regimen designed in our previous study may substantially enhance the ability of ventilation-perfusion matching during exercise, which effects are accompanied by an improved global and disease-specific QoL in HF patients. Conversely, the traditional MCT regimen may only maintain these physiologic responses to exercise at pre-interventional status. By elucidating the relationship between physical activity and hemodynamic property, this review attempts to provide a CR strategy for developing suitable exercise prescription that ameliorates hemodynamic disturbance, further retarding the disease progression and improving health-related QoL in patients with HF.

**Key Words:** Aerobic capacity • Heart failure • Hemodynamics • Rehabilitation

## BENEFICIAL EFFECTS OF CARDIAC REHABILITATION (CR) IN HEART FAILURE (HF)

Cardiovascular disease is the second highest cause of mortality in the Taiwanese population, at approximately 11.1%.[1] As the end stage of cardiovascular disease nears, HF patients suffer a higher rate of morbidity and have a generally poor prognosis.[2] According to the report in 2009, the hospitalization cost of HF in the United States for those aged 65 years or older at $20.1 billion.[3] Hence, healthcare associated with HF subjects the medical system to a substantial burden.

CR is suitable for patients with acute myocardial infarction (AMI), post myocardial revascularization or cardiac transplantation, and also for those patients with stable chronic angina and chronic cardiac insufficiency.[4] By modifying health behavior, this medical strategy can effectively improve physical and psychological well-being, help patients recover productive participation and function in society, and further minimize disease progression in patients with cardiovascular disorders.[5] Additionally, CR also reduces the detrimental effects associated with cardiac events to prevent patients with HF from recurrent hospitalization, eventually reducing

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healthcare costs.[6-9] As a multidisciplinary intervention, CR involves exercise therapeutics, medication, smoking cessation, nutritional counseling, and psychological aid.[10] Moreover, the ability of CR to succeed in eventually controlling cardiovascular risk factors is mainly determined by the efficacy of physical exercise-based therapy.[11] Compared to usual care without exercise, recent studies of meta-analyses demonstrated that CR with an emphasis on exercise therapeutics was associated with a decrease of 20%-30% in the mortality rate.[11,12] Therefore, this review article focuses on current exercise strategies in HF healthcare according to the opinion of a physiatrist. Table 1 shows the overview of candidates and contraindication for cardiac rehabilitation.[4,13]

## IMPROVING CR REFERRAL AND PARTICIPATION

Low referral and participation rates are critical issues in the successful delivery of CR. Sundararajan et al. have reported that the attendance rates of CR were 14%~37% in Victoria, Australia.[14] In America, Blackburn et al. indicated that only 11% of patients participated in a hospital-based CR program in the Cleveland Clinic Foundation, United States,[15] whereas Norris et al. showed that 28.9% of patients were referred to CR in Alberta, Canada.[16] In Taiwan, only 18~33% of patients received outpatient CR within six months following coronary bypass graft or valvular surgery, even if these patients lived in modern cities with convenient mass transportation.[17]

When the American Heart Association's "Get with The Guidelines (GWTG)" program was implemented, the referral rate for CR was markedly elevated in patients with coronary artery disease[18] and in patients with AMI by 56% and 55%, respectively.[19] The GWTG program paid attention to how first-line cardiologists refer eligible patients to CR before discharge. Although the overall CR referral rate was still low, this program actually represented an improvement compared to earlier data.[12-15]

**Table 1.** Overview of cardiac rehabilitation

| | |
|---|---|
| Candidate of cardiac rehabilitation | |
| CAD | |
| MI | |
| PTCA | |
| CABG | |
| HF | |
| Heart transplant | |
| Pacemaker, ICD, RCT | |
| Effect of exercise training on cardiac risk factors[12] | |
| DM | Decrease in hemoglobin A1C of 0.8% |
| Dyslipidemia | Increase in high-density lipoprotein of 2.5 mg/dL |
| Hypertension | Reduction in blood pressure of 3.4/2.4 mm Hg |
| Smoking | Higher levels of abstinence from smoking |
| Obesity | 6.7-kg weight loss at 1 year |
| Psychosocial health | Decreases in depression, anxiety, hostility, somatization, and psychosocialstress |
| Contraindication of Cardiac Rehabilitation[3] | |
| A recent significant change in the resting ECG suggesting significant ischemia, recent MI (within 2 days), or other acute cardiac event | |
| Unstable angina | |
| Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise | |
| Symptomatic severe aortic stenosis | |
| Uncontrolled symptomatic HF | |
| Acute pulmonary embolus or pulmonary infarction | |
| Acute myocarditis or pericarditis | |
| Suspected or know dissecting aneurysm | |
| Acute systemic infection, accompanied by fever, body aches, or swollen lymph glands | |

CABG, coronary artery bypass graft; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; ICD, implantable cardiac defibrillator; MI, myocardial infarction; PTCA, percutaneous coronary angioplasty; RCT, cardiac resynchronization therapy.

On the other hand, the studies of Gravely-Witte et al.[20] and Grace et al.[21] indicated that the automatic referral and liaison strategies performed by healthcare providers and early outpatient education increased the CR referral rate by over 80%. These aforementioned investigations support the proposition that physicians and other healthcare providers including case managers and physical therapists play important roles as modulators in early CR access and a successful CR referral system. In Taiwan, the Heart Failure Center (HFC), Keelung Chang Gung Memorial Hospital (CGMH) effectively applied the automatic referral system to recruit core team members when patients were admitted, and then started consequent education course and liaison work during hospitalization. Afterwards, these eligible patients would refer to the rehabilitation department. Thereafter, the CR referral mechanism was able to achieve up to and even > 90 % efficacy rate.

## EXERCISE TESTING FOR HF

The cardiopulmonary exercise test (CPET) is a useful tool to evaluate patient exercise capacity and exertional symptoms using objective measures.[22-24] This test can offer numerous physiologic parameters including ventilatory, hemodynamic, and metabolic responses to exercise, which may reflect on underlying mechanisms of exertional dyspnea, angina pectoris, and fatigue in patients with cardiovascular disorders (Table 2).[22,25] Even in patients with arrhythmia or users of β-adrenergic blocker, the CPET can also provide highly reproducible results of exercise performance and limitation.[26] Furthermore, the ventilatory parameters obtained from CPET may contain information about disease prognosis. Peak oxygen consumption ($VO_{2peak}$) and oxygen uptake efficiency slope (OUES) are the surrogates of exercise capacity and efficiency, respectively.[27] The $V_E$-$VCO_2$ slope is a powerful predictor of survival in cardiac patients; namely, a slope number over 34 may represent a worse prognosis.[27] Besides, periodic breathing, an abnormal pattern of respiration that consists of alternating hyperpnea and hypopnea, has been recognized during exercise in chronic HF patients.[28] Notably, these indices of ventilatory efficiency may be correlated with exercise-induced central and peripheral hemodynamic changes.[29]

Recently, the HFC in Keelung CGMH first integrated a novel bioreactance-based measurement (noninvasive continuous cardiac output monitoring system, NICOM), near-infrared spectroscopy, and automatic gas analysis to identify the involvement of ventilatory and cardiac-cerebral-muscle hemodynamic responses to exercise in functional impairment in patients with HF (Figure 1).[29] The results of this study clearly demonstrated that the suppression of cerebral and muscle hemodynamics during exercise were associated with ventilatory abnormality, which reduced functional capacity in patients with HF.[29] A subsequent investigation further found that less than 4.5 L/min/$m^2$ of peak cardiac index was a signifi-

**Table 2.** Parameters in CPET and its clinical implication

| | Change in HF | Cut-off value | Clinical implication |
|---|---|---|---|
| $VO_{2max}$ | ↓ | 14 cc/min/kg | Aerobic capacity<br>Functional fitness<br>Prognosis prediction |
| OUES | ↓ | (not yet) | Surrogate of $VO_{2max}$ in submaximal exercise test |
| Ve-$VCO_2$ slope | ↑ | 34 | Exertional hyperventilation<br>More powerful survival prediction than $VO_{2max}$ |
| $VO_2$ at AT | ↑ | - | Aerobic capacity<br>Functional fitness |
| CI | ↓ | 4.5 L/min/$m^2$ | Predictor on composite events of rehospitalization and death in HF |
| EPB | prevalence↑ | - | Survival prediction<br>Sleep apnea correlation |

AT, anaerobic threshold; CI, cardiac index (cardiac output/body surface area); EPB, exercise periodic breathing; OUES, oxygen uptake efficiency slope; $VeVCO_2$ slope, minute ventilation versus carbon dioxide production slope; VO2, oxygen consumption; $VO2_{max}$, maximal oxygen consumption.

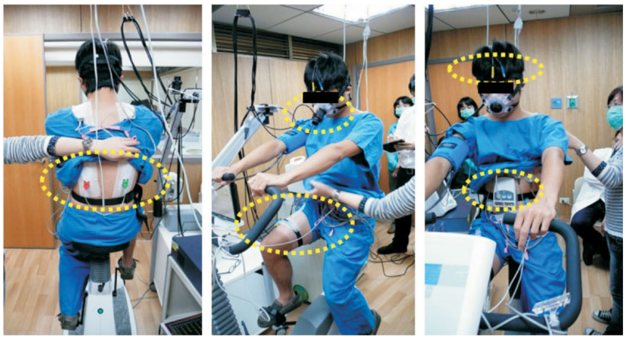

***Figure 1.*** *Integrated a novel bioreactance-based measurement (non-invasive continuous cardiac output monitoring system, NICOM) (left panel), near-infrared spectroscopy (NIRS) (upper circle in right panel and lower circle in middle panel), electrocardiogram (lower circle in right panel) and automatic gas analysis (upper circle of middle panel) to identify the involvement of ventilatory and cardiac-cerebral-muscle hemodynamic responses to exercise in patients with HF.*

cant predictor regarding the composite events of rehospitalization and death in HF patients.[30]

## EXERCISE PRESCRIPTION FOR HF

Exercise prescription aims to enhance physical fitness, promote health by reducing risk factors for cardiovascular disease, and ensure safety during exercise. The principal components of a systematic, individual exercise prescription comprise an appropriate type, intensity, duration, frequency, and progression of exercise.[4]

### Type of exercise

Aerobic endurance training that comprises isotonic and rhythmic exercise using large muscles has been proposed to be part of an effective rehabilitation strategy for HF patients. This exercise regimen in outpatient cardiac patients is typically performed at moderate intensity for at least 30 min,[31] and has been associated with an increased $VO_{2peak}$ of 11-36%.[32]

Aerobic interval training (AIT), that includes alternating high- and low-intensity exercise sessions, is a more effective modality for improving functional capacity than traditional endurance training in patients with HF.[33-35] Use of an animal model of post-infarction HF has shown that AIT rescued impaired contractility, attenuated hypertrophy, and reduced expression of atrial natriuretic peptide in cardiac myocytes.[36,37] The authors' recent investigation also demonstrated that AIT was superior to moderate continuous training (MCT) for enhancing ventilatory and central/peripheral hemodynamic responses to exercise in patients with HF.[38]

In a recent development in HF rehabilitation, strength training has been recommended to counter cachexia-related disability.[39] This training may increase muscle mass and strength, subsequently improving functional mobility in patients with HF. However, isometric or eccentric resistance exercise should be avoided (or performed with great care) because of the resultant increase in cardiac afterload.[40]

Evidence to date strongly suggests that poor inspiratory muscle performance is associated with dyspnea, exercise intolerance, and functional impairment in patients with HF.[41] Inspiratory muscle training may be beneficial for increasing inspiratory muscular strength and endurance, alleviating dyspnea, and improving functional status in HF patients.[42]

### Intensity, duration, and frequency of exercise

According to recommendations by the Center for Disease Control and Prevention and the American College of Sports Medicine (ACSM), exercise intensity is the primary factor when prescribing an exercise regimen to protect individuals against cardiovascular disease.[4] The optimal exercise prescription for an individual is based on an objective evaluation of the individual's response to exercise, including heart rate (HR), rating of perceived exertion (RPE), $VO_2$, and metabolic equivalents during a graded exercise test.[4] Cardiac patients can use a HR/EKG monitor to obtain the assigned intensity of exercise. Additionally, the Borg 6-to-20 scale is used to assess the RPE during each exercise session. However, patients should be instructed to immediately stop exercise training if they have chest pain or other cardiac symptom/sign.

In general, the intensity of exercise has a diversity of setting ranged from 40% to 80% $VO_{2peak}$.[4] In the HFC in Keelung CGMH, the HF patients performed two supervised hospital-based training programs on a bicycle ergonometer (Figure 2), completing three weekly sessions for 12 weeks. The exercise protocol in traditional MCT comprised a warm-up at 30% of $VO_{2peak}$ [≈ 30% heart rate reserve (HRR); ≈ 30%·($HR_{peak}$ – $HR_{rest}$) + $HR_{rest}$] for 3 min, followed by continuous 60% of $VO_{2peak}$ (≈ 60% HRR) for 30 min, then a cool-down at 30% of $VO_{2peak}$ for

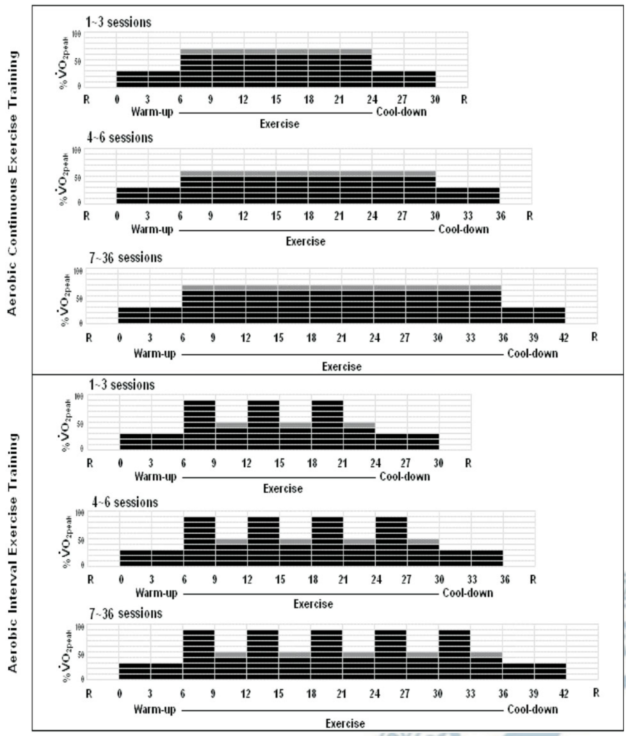


*Figure 2.* *Schematic figure of the content of exercise training, including warm-up phase, exercise phase and cool-down phase; and the training intensity and progression of moderate continuous training (MCT) (upper panel) aerobic interval training (AIT) (lower panel).*

3 min. From 2011 to date, a novel AIT regimen has been successfully applied to HF patients, which comprised warm-up for 3 min at 30% of $VO_{2peak}$ before exercise, and five 3-minute intervals at 80% of $VO_{2peak}$ (≈ 80% HRR). Each interval was separated by 3-minute exercise at 40% of $VO_{2peak}$ (≈ 40% HRR). The exercise session was terminated by a 3-minute cool-down period at 30% of $VO_{2peak}$. Although the two protocols were isocaloric at the same exercise duration, AIT rather than MCT effectively improved oxygen uptake efficiency by enhancing hemodynamics and suppressed oxidative stress/inflammation associated with cardiac dysfunction in patients with HF.[38]

## HEALTH-RELATED QUALITY OF LIFE IMPROVED BY CR

According to the authors' investigations, both AIT and MCT decreased patient scores on the Minnesota Living with Heart Failure questionnaire, whereas only AIT significantly increased patient scores on the Short Form-36 Health Survey questionnaire of physical and mental dimensions.[38,43] These findings imply that AIT rather than MCT simultaneously improves generic and disease-specific quality of life (QoL) in patients with HF. A possible explanation of the superior effects of AIT on these health-related QoL issues is that AIT effectively enhances aerobic capacity and efficiency and relieves exercise intolerance. This increases the ability of patients to cope with the physical demands of daily activity, and subsequently improves psychosocial status in HF patients. Furthermore, an improved health-related QoL could exhibit a reduced potential for mortality in HF patients,[44] and simultaneously reduce the financial burden to the Taiwanese health care system.[45]

## CONCLUSIONS

HF is a major cardiovascular syndrome with an increasing incidence and prevalence, which may accelerate physical deconditioning and the consequent vicious cycle of numerous associated disorders.[2] However, HF patients on optimal cardiovascular pharmacologic therapy frequently remain burdened by dyspnea and exercise intolerance.[2] Successful CR is a valuable non-pharmacologic intervention for improving aerobic fitness and overall health status in patients with HF.[46] The automatic referral and liaison strategies performed by healthcare providers and early outpatient education can significantly increase the referral rate of CR.[20] However, controversy persists regarding the type and volume of CR that optimally promotes beneficial adaptations in ventilatory and hemodynamic functions. A novel AIT regimen noted in our previous study may effectively improve ventilatory and hemodynamic efficiencies during exercise, which effects are accompanied by improved global and disease-specific QoL in patients with HF.[38] Conversely, the traditional MCT regimen may only maintain these physiologic responses to a level of exercise similar to pre-interventional status. These findings provide a new insight into the larger effect of AIT on ventilation-perfusion matching during exercise, and may have important implications for exercise training in HF rehabilitation.

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## REFERENCES

1. Department of Health: the leading cause of death, 2012. Available from http://health99.Doh.Gov.Tw/txt/healthyheadlinezone/healthyheadlinedetai.Aspx?Topicno=6798.
2. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American college of cardiology foundation/american heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. *Circulation* 2009;119:e391-479.
3. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics –– 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:e21-181.
4. American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Philadelphia: Lippincott Williams & Wilkins, 2010.
5. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the american heart association. *Circulation* 2001;104:1694-740.
6. P.RE.COR. GROUP, Leizoroviez A, Saint-Pierre A, et al. Comparison of a rehabilitation programme, a counselling programme and usual care after an acute myocardial infarction: results of a long-term randomized trial. Eur Heart J 1991;12:612-6.
7. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med* 2001;345:892-902.
8. Levin LA, Perk J, Hedbäck B. Cardiac rehabilitation — a cost analysis. *J Intern Med* 1991;230:427-34.
9. Wong WP, Feng J, Pwee KH, Lim J. A systematic review of economic evaluations of cardiac rehabilitation. *BMC Health Serv Res* 2012;12:243.
10. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007;115:2675-82.
11. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004;116:682-92.
12. Ricardo DR, Araújo CGSd. Reabilitação cardíaca com ênfase no exercício: uma revisão sistemática (exercise-based cardiac rehabilitation: a systematic review). *Rev Bras Med Esporte* 2006;12:279-85.
13. Metkus TS Jr, Baughman KL, Thompson PD. Exercise prescription and primary prevention of cardiovascular disease. *Circulation* 2010;121:2601-4.
14. Sundararajan V, Bunker SJ, Begg S, et al. Attendance rates and outcomes of cardiac rehabilitation in Victoria, 1998. *Med J Aust* 2004;180:268-71.
15. Blackburn GG, Foody JM, Sprecher DL, et al. Cardiac rehabilitation participation patterns in a large, tertiary care center: evidence for selection bias. *J Cardiopulm Rehabil* 2000;20:189-95.
16. Norris CM, Jensen LA, Galbraith PD, et al. Referral rate and outcomes of cardiac rehabilitation after cardiac catheterization in a large canadian city. *J Cardiopulm Rehabil* 2004;24:392-400.
17. Liu DH, Chen YC, Hung SY, et al. Cardiac rehabilitation after coronary artery bypass graft or heart valve replacement surgery-experience of a medical center. *Tw J Phys Med Rehabil* 2013;41:181-8.
18. Brown TM, Hernandez AF, Bittner V, et al. Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the american heart association's get with the guidelines program. *J Am Coll Cardiol* 2009;54:515-21.
19. Mazzini MJ, Stevens GR, Whalen D, et al. Effect of an american heart association get with the guidelines program-based clinical pathway on referral and enrollment into cardiac rehabilitation after acute myocardial infarction. *Am J Cardiol* 2008;101:1084-7.
20. Gravely-Witte S, Leung YW, Nariani R, et al. Effects of cardiac rehabilitation referral strategies on referral and enrollment rates. *Nat Rev Cardiol* 2010;7:87-96.
21. Grace SL, Angevaare KL, Reid RD, et al. Effectiveness of inpatient and outpatient strategies in increasing referral and utilization of cardiac rehabilitation: a prospective, multi-site study. *Implementation Sci* 2012;7:120.
22. Mezzani A, Agostoni P, Cohen-Solal A, et al. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the exercise physiology section of the european association for cardiovascular prevention and rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2009;16:249-67.
23. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the american heart association. *Circulation* 2010;122:191-225.
24. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease.

*Circulation* 2011;123:668-80.
25. Ridgway ZA, Howell SJ. Cardiopulmonary exercise testing: a review of methods and applications in surgical patients. *Eur J Anaesthesiol* 2010;27:858-65.
26. Dufay-Bougon C, Belin A, Dahdouh ZS, et al. The prognostic value of the cardiopulmonary exercise test in patients with heart failure who have been treated with beta-blockers. *Turk Kardiyol Dern Ars* 2013;41:105-12.
27. Van de Veire NR, Van Laethem C, Philippé J, et al. VE/VCO2 slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVO2. *Eur J Cardiovasc Prev Rehabil* 2006;13:916-23.
28. Wang JS, Fu TC, Wang CH, et al. Exertional periodic breathing potentiates erythrocyte rheological dysfunction by elevating pro-inflammatory status in patients with anemic heart failure. *Int J Cardiol* 2013;167:1289-97.
29. Fu TC, Wang CH, Hsu CC, et al. Suppression of cerebral hemodynamics is associated with reduced functional capacity in patients with heart failure. *Am J Physiol Heart Circ Physiol* 2011; 300:H1545-55.
30. Lee MF, Chen WS, Fu TC, et al. Non-invasive cardiac index monitoring during cardiopulmonary functional testing provides additional prognostic value in patients after acute heart failure. *Int Heart J* 2012;53:364-9.
31. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the american heart association. *Circulation* 2001;104: 1694-740.
32. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American heart association scientific statement from the council on clinical cardiology (subcommittee on exercise, cardiac rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity), in collaboration with the american association of cardiovascular and pulmonary rehabilitation. *Circulation* 2005;111:369-76.
33. Moholdt TT, Amundsen BH, Rustad LA, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J* 2009;158:1031-7.
34. Rognmo Ø, Hetland E, Helgerud J, et al. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004;11:216-22.
35. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 2007;115:3086-94.
36. Crimi E, Ignarro LJ, Cacciatore F, Napoli C. Mechanisms by which exercise training benefits patients with heart failure. *Nat Rev Cardiol* 2009;6:292-300.
37. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. *Circulation* 2010;122:1221-38.
38. Fu TC, Wang CH, Lin PS, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *Int J Cardiol* 2013; 167:41-50.
39. Esposito F, Reese V, Shabetai R, et al. Isolated quadriceps training increases maximal exercise capacity in chronic heart failure: the role of skeletal muscle convective and diffusive oxygen transport. *J Am Coll Cardiol* 2011;58:1353-62.
40. Braverman DL. Cardiac rehabilitation: a contemporary review. *Am J Phys Med Rehabil* 2011;90:599-611.
41. Cahalin LP, Arena R, Guazzi M, et al. Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes. *Expert Rev Cardiovasc Ther* 2013;11:161-77.
42. Laoutaris I, Dritsas A, Brown MD, et al. Inspiratory muscle training using an incremental endurance test alleviates dyspnea and improves functional status in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2004;11:489-96.
43. Wang JS, Fu TC, Lien HY, et al. Effect of aerobic interval training on erythrocyte rheological and hemodynamic functions in heart failure patients with anemia. *Int J Cardiol* 2013;168:1243-50.
44. Georgiou D, Chen Y, Appadoo S, et al. Cost-effectiveness analysis of long-term moderate exercise training in chronic heart failure. *Am J Cardiol* 2001;87:984-8.
45. Carvalho VO, Mezzani A. Aerobic exercise training intensity in patients with chronic heart failure: principles of assessment and prescription. *Eur J Cardiovasc Prev Rehabil* 2011;18:5-14.
46. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1439-50.