Role of cardiopulmonary stress testing in heart failure management

Nandini Nair MD PhD, Enrique Gongora MD

Introduction

Heart failure (HF) is a global problem of epidemic proportions. In the United States HF affects more than 5 million people currently, with 500,000 newly diagnosed cases every year. It is a syndrome of multiple etiologies and can involve systolic and/or diastolic dysfunction. The risk of death due to HF has increased partly because advances in technology have decreased the age-adjusted death rates for cardiac diseases, especially those of ischemic origin, and, therefore, increased the prevalence of HF through longer survival.

Direct measurement of ventilation and gas exchange during exercise is called a cardiopulmonary stress test (CPX). Cardiopulmonary stress testing measures multiple parameters that vary with alterations in cardiac and pulmonary function. The most important variables are expiratory ventilation ($\dot{V}E$), pulmonary gas exchange expressed as oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), cardiac rate and rhythm, and blood pressure. A composite set of variables measured by CPX links cardiovascular and pulmonary responses to the metabolic demands of exercise. Exercise intolerance is a characteristic feature of HF with symptoms, such as shortness of breath, fatigue, or both, which are usually out of proportion to the level of exertion. Therefore, the assessment of exercise intolerance can be used to predict the degree of cardiac impairment, stratify risk, and optimize therapy.

The use of CPX in HF patients began with the classic investigation by Mancini *et al* in 1991.[1] Currently, CPX is used for diagnosis, risk stratification, and prognostication (Figure 1).[1-5] This review focuses on use of CPX in the assessment of disease severity and clinical management of HF with reduced ejection fraction (HFrEF) as well as preserved ejection fraction (HFpEF).

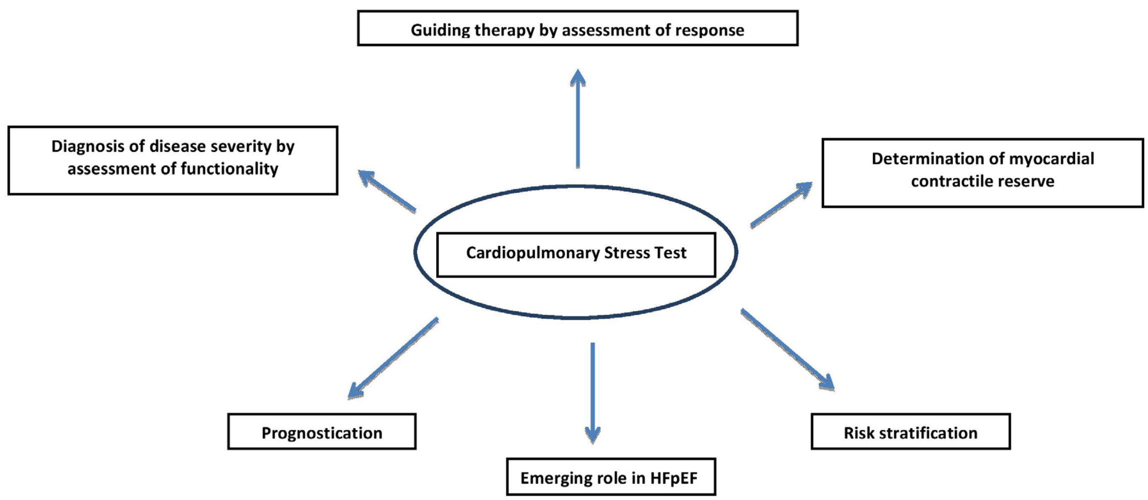
Cooresponding Author : Nandini Nair MD PhD
Author Contact Information: Nandini.nair@ttuhsc.edu
DOI: 10.12746/swrccc2016.0415.207

Assessment of disease severity, risk stratification, and prognostication

In HFrEF the most important use of CPX is to triage patients at the appropriate time to advanced HF therapies, such as implantation of ventricular assist devices (VADs) and cardiac transplantation. In HFpEF it is used to determine disease severity by unmasking symptoms with exercise. In both cases it is also used to guide management toward optimal medical regimens or to triage to advanced surgical therapies for HF.

The New York Heart Association (NYHA) functional class is a subjective classification addressing a patient's functional capacity.[6] To overcome the subjectivity of this classification exercise testing, such as CPX, has been used to make objective decisions about the treatment of chronic HF.[7] Peak oxygen consumption ($\dot{V}O_2$) has been shown to correlate with functional capacity and mortality. This relationship between oxygen consumption and outcomes was first reported by Mancini *et al*.[1] More recently, other measurements obtained during metabolic exercise tests have been shown to predict mortality in patients with end stage HF. The slope of the relationship between ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope), the end tidal carbon dioxide (CO_2), the oxygen uptake efficiency slope (OUES), and the rate of heart

Figure 1 Uses of Cardiopulmonary Stress Tests in Heart failure



rate recovery have all been found to be useful predictors of outcome.[8-10] Russell *et al* showed that the NYHA functional class predicts exercise parameters and can be used for assessing disease severity and outcomes.[11] The study by Russell also demonstrated that there is a significant difference in the peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, and exercise time in patients with NYHA functional class II symptoms compared to those with NYHA functional class III/IV symptoms.[11]

In the era of evidence-based medicine, risk stratification using multivariable scores has reliable, robust scores using CPX as one of the parameters.[15-22] The Heart Failure Survival Score by Aaronson *et al* has proved to be better than using peak oxygen consumption alone.[18] The score by Myers *et al*[16,17] also used $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, end-tidal CO_2 pressure, OUES, and heart rate recovery. The $\dot{V}E/\dot{V}CO_2$ slope was the strongest predictor of cardiovascular risk for mortality. Poor ventilatory control in heart failure can manifest as a crescendo-decrescendo pattern without interposed apnea called exercise oscillatory ventilation (EOV). Peak circulatory power is the product of peak $\dot{V}O_2$ and peak systolic blood pressure. Therefore addition of these extra parameters such as Exercise Oscillatory Ventilation (EOV), the lowest $\dot{V}E/\dot{V}CO_2$ ratio, peak circulatory power, $\dot{V}E/\dot{V}CO_2$ slope, and OUES, produced an optimal score for predicting the risk for mortality in this population.[23,24]

Exercise ventilatory power (EVP) is the ratio between peak systolic blood pressure and the $\dot{V}E/\dot{V}CO^2$ slope. Forman *et al*[25] showed that using ≤ 3.5 mmHg for the EVP as a cutoff for high risk had better prognostic discrimination capability and predict survival. Subsequently, Borghi-Silva *et al*[26] used Doppler echocardiographic recordings throughout the CPX tests in patients with HFrEF and showed that lower EVPs indicated severely impaired peak $\dot{V}O_2$ and cardiac output response to exercise with consequent impairment of right heart function and hemodynamics affecting the pulmonary system. This result showed that a lower EVP indicated increased disease severity.

The relative increase in $\dot{V}O_2$ to maximal work rate (WR) (change in $\dot{V}O_2$/change in WR) has been proposed as an indicator of cardiac efficiency and aerobic generation of adenosine triphosphate. In normal subjects this increases linearly and represents a surrogate index of cardiac output. In ventricular dysfunction during exercise, this parameter may plateau and fail to reach a value ≥ 10 mL/min/W. Additionally, a flat $\Delta \dot{V}O_2/\Delta WR$ was associated with increased systolic pulmonary artery pressure and decreased RV systolic function.[27,28]

The Exertional Oscillatory Ventilation (EOV) has been found to be an important prognostic index in HF. The pathophysiological mechanisms of EOV are still not fully understood. Several factors, including decreased cardiac output, suboptimal chemoreceptor responses, reduced ventilator control, RV dysfunction, abnormal pulmonary hemodynamics, and delayed information transfer related to arterial CO_2 levels from the pulmonary capillaries to peripheral and central chemoreceptors secondary to impaired ventricular function, probably affect the EOV. Hence, the addition of EOV to CPX parameters would be useful for better risk stratification and prognostication. The utilization of the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score for prognostication helps identify cardiovascular mortality and the requirement of heart transplantation. The MECKI score consists of six laboratory values, such as hemoglobin, sodium, creatinine clearance calculated by the Modification of Diet in Renal Disease (MDRD) equation, the left ventricle ejection fraction (LVEF), the percentage of $\dot{V}O_2$ max, and the $\dot{V}E/\dot{V}CO_2$ slope.[29-38]

Respiratory muscle performance (RMP) has emerged to be an important factor in risk stratifying patients with chronic HF. The strong association of RMP to indices of pulmonary vascular hemodynamics is valuable in the context of a plateau in change in $\dot{V}O_2$/change in WR. However, measurement of RMP has limitations. Despite these challenges RMP still appears to have a role in patients with HF for diagnosis, prognosis, and therapy.[39-47]

Determination of myocardial contractile reserve

The strongest correlation with $\dot{V}O_2$ max was with the peak left ventricular systolic tissue velocity (S') during exercise. Resting echocardiographic parameters, like the ejection fraction of the left ventricle, correlated poorly with exercise capacity. In idiopathic dilated cardiomyopathy, $\dot{V}O_2$ max reflected myocardial contractile reserve in ambulatory patients. However, the slope of $\dot{V}E/\dot{V}CO_2$ was not useful in this population. In another study with non- ischemic cardiomyopathy patients, BNP and left ventricular inotropic reserve correlated well with CPX.[48-50]

Use of CPX for guiding therapy

The use of CPX in HFrEF and HFpEF is well documented in the current literature. Some representative studies are listed in Table 1. The use of CPX has been demonstrated in both patients with HFrEF and those with HFpEF to help with risk stratification and prognostication. Figure 2 shows a suggested algorithm for using CPX to risk stratify and guide management of HF.

The Ventilatory Threshold (VT), also called the anaerobic threshold, assesses exercise intensity, ventilation, and metabolism and has potential use in therapeutic interventions. In HF, aerobic exercise training should be performed below the VT. Intermittently, exercise above VT can be done but with caution.[51,52] Hence assessment of VT can be used to determine exercise prescriptions in HF. In a small study CPX guided exercise rehabilitation was safe and effective for patients with HF.[53]

Summary

Cardiopulmonary exercise testing has evolved considerably since the first report of its use in HF in 1991. The test has multiple uses in HF, including defining right ventricular failure and secondary pulmonary hypertension.[54-56] Multiple small studies have demonstrated the utility of CPX in diagnosis, risk stratification for mortality, and prognostication of HFrEF and HFpEF The use of CPX in grading diastolic dysfunction has been reported in a small study of individuals with HFpEF.[57] Future research investigations may be needed to conclusively include the newer parameters discussed (EOV, OUES, EVP and circulatory power) before these can be used routinely in CPX assessments.[58] CPX is, therefore, a highly useful, comprehensive test to evaluate, risk stratify, and guide therapy in the present day management of HF.

Keywords: Cardiopulmonary stress test, HFpEF, HFrEF, $\dot{V}O_2$ max, $\dot{V}E/\dot{V}CO_2$

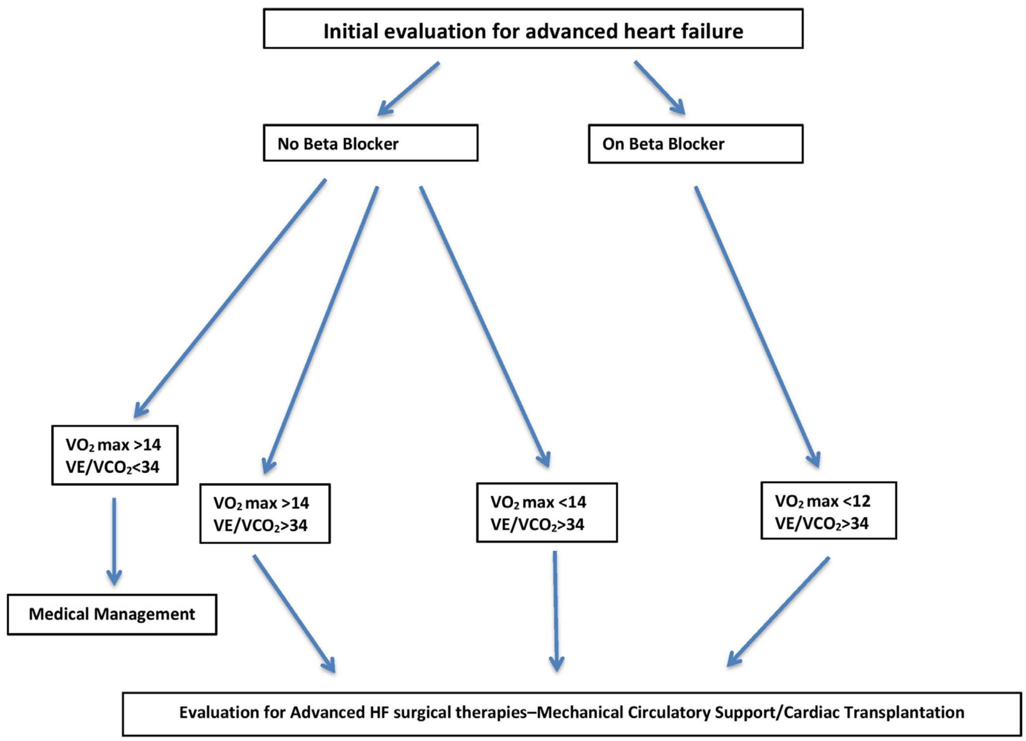
Author Affiliation: Nandini Nair is a transplant cardiologist in the Department of Internal Medicine/Division of Cardiology at Texas Tech University Health Sciences Center in Lubbock, TX. Enrique Gongora is a cardiothoracic /transplant surgeon at Memorial Cardiac and Vascular Institute in Hollywood, FL.
Received: 03/10/2015
Accepted: 06/18/2016
Reviewers: Aliakbar Arvandi MD
Published electronically: 07/15/2016
Conflict of Interest Disclosures: None

Table 1 : Selected studies investigating utility of CPX in HFrEF and HFpEF

Study	Study Type	Type of HF	Subjects (n)	Conclusions
Borghi-Silva et al[26] 2014	Prospective	HFrEF	86	Lower EVP suggests higher disease severity
Foreman et al[25] 2012	Prospective	HFrEF	875	Ventilatory power was the strongest prognostic factor
Bandera et al [28] 2014	Prospective	HFrEF, HFpEF	136	A flat $\Delta VO_2/\Delta WR$ reflects impaired functional phenotype
Lewis et al [54] 2008	Prospective	HFrEF	30	Significant correlation between VE/VCO_2 and PVR , RVEF
Moore et al [55] 2007	Prospective	HFrEF, HFpEF	147	VE/VCO_2 slope is significantly higher in patients with SHF compared with DHF
Kitte et al [56] 2006	Prospective	HFrEF, HFpEF	216	Patients with DHF have exercise tolerance between that of patients with SHF and controls
Guazzi et al [57] 2010	Prospective	HFpEF	22	CPX parameters can be used for assessment of the degree of DD

SHF-systolic HF, DHF-diastolic HF, DD-diastolic dysfunction, HRrEF-heart failure with reduced ejection fraction, HFpEF-heart failure with preserved ejection fraction

Figure 2 Suggested algorithm for risk stratification in advanced heart failure



REFERENCES

1. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83:778–786.
2. Wada O, Asanoi H, Miyagi K, Ishizaka S, Kameyama T, Seto H, Sasayama S. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J* 1993; 125:790–798.
3. Arena R, Myers J, Guazzi M. Ventilatory abnormalities during exercise in heart failure: a mini review. *Curr Resp Med Rev* 2007; 3:179–187.
4. Myers J Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. *Int J Sports Med* 2005; 26(Suppl 1):S49–S55.
5. Rostagno C, Galanti G, Comeglio M, Boddi V, Olivo G, Neri Serneri G. Comparison of different methods of functional evaluation in patients with chronic heart failure. *Eur J Heart Fail* 2000; 2:273-80.
6. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed Little, Brown & Co; Boston, Mass: 1994. pp. 253–256.
7. Fleg JL, Pina IL, Balady GJ, Chaitman BR, Fletcher B, Lavie C, Limacher MC, Stein RA, Williams M, Bazzarre T. Assessment of functional capacity in clinical and research applications. An advisory from the Committee on Exercise, Rehabilitation, and Prevention Council on Clinical Cardiology, American Heart Association. *Circulation* 2000; 102:1591–1597.
8. Myers J, Arena R, Dewey F, Bensimhon D, Abella J, Hsu L, Chase P, Guazzi M, Peberdy MA. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J* 2008; 156:1177–83.
9. Genth S, Zotz R, Darius H, Treese N, Sigmund M, Hanrath P, Meyer J. Comparison of NYHA classification with cardiopulmonary function in patients with chronic heart failure. *Z Kardiol* 1996; 85:428-34.
10. Guazzi M, Labate V, Cahalin LP, Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease se-

verity in heart failure patients with reduced and preserved ejection fraction. *Eur J Prev Cardiol* 2014; 21:847-54.

11. Russell SD, Saval MA Robbins JL, Ellestad MH, Gottlieb SS, Handberg EM, Zhou Y Chandler B, and the HF-ACTION Investigators. New York Heart Association functional class predicts exercise parameters in the current era *Am Heart J* 2009 Oct; 158(4 Suppl): S24–S30.

12. Ashley E, Myers J, Froelicher VF. Exercise testing scores as an example of better decisions through science. *Med Sci Sports Exerc* 2002; 34: 1391–1398.

13. Swets JA, Dawes RM, Monahan J. Better decisions through science. *Sci Am* 2000; 283: 82–87.

14. Koopman RJ, Mainous AG3rd. Evaluating multivariate risk scores for clinical decision making. *Fam Med* 2008; 40: 412–416.

15. Ingle L, Rigby AS, Sloan R, et al. Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart* 2014; 100: 781–786.

16. Myers J, Arena R, Dewey F, *et al*. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J* 2008; 156: 1177–1183.

17. Myers J, Oliveira R, Dewey F, *et al*. Validation of a cardiopulmonary exercise test score in heart failure. *Circ Heart Fail* 2013; 6: 211–218.

18. Aaronson KD, Schwartz SJ, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997; 95: 2660–2667.

19. Lund LH, Aaronson KD, Mancini DM. Validation of peak exercise oxygen consumption and the Heart Failure Survival Score for serial risk stratification in advanced heart failure. *Am J Cardiol* 2005; 95: 734–741.

20. Zugck C, Krüger C, Kell R, e*t al*. Risk stratification in middle-aged patients with congestive heart failure: prospective comparison of the Heart Failure Survival Score (HFSS) and a simplified two-variable model. *Eur J Heart Fail* 2001; 3: 577–585.

21. Guazzi M, Boracchi P, Arena R, *et al*. Development of a cardiopulmonary exercise prognostic score for optimizing risk stratification in heart failure: the (P)e(R)i(O)dic (B)reathing during (E)xercise (PROBE) study. *J Card Fail* 2010; 16: 799–805.

22. Agostoni P, Corrà U, Cattadori G, *et al*. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013; 167: 2710–2718.

23. Ingle L, Rigby, AS, Sloan R, *et al*. Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart* 2014; 100: 781–786.

24. Ingle L. Prognostic value and diagnostic potential of cardiopulmonary exercise testing in patients with chronic heart failure. *Eur J Heart Fail* 2008; 10: 112–118.

25. Forman, DE, Guazzi, M, Myers J, *et al*. Ventilatory power: a novel index that enhances prognostic assessment of patients with heart failure. *Circ Heart Fail* 2012; 5:621–626.

26. Borghi-Silva A, Labate, V, Arena R, *et al*. Exercise ventilatory power in heart failure patients: Functional phenotypes definition by combining cardiopulmonary exercise testing with stress echocardiography. *Int J Cardiol* 2014; 176: 1348–1349.

27. 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.

28. Bandera F, Generati G, Pellegrino M, *et al*. Role of right ventricle and dynamic pulmonary hypertension on determining $\Delta\dot{V}O2/\Delta$Work Rate flattening: insights from cardiopulmonary exercise test combined with exercise echocardiography. *Circ Heart Fail* 2014;7:782-90.

29. Guazzi M. Abnormalities in cardiopulmonary exercise testing ventilatory parameters in heart failure: pathophysiology and clinical usefulness. *Curr Heart Fail Rep* 2014;11:80-7

30. Guazzi M, Adams V, Conraads V, *et al*. EACPR/AHA Scientific Statement. Clinical recommendations for cardio pulmonary exercise testing data assessment in specific patient populations. *Circulation* 2012; 126:2261-74.

31. Corra U, Giordano A, Bosimini E, *et al*. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest* 2002; 121:1572-80.

32. Corrà U. Exercise oscillatory ventilation in heart failure I*nt J Cardiol* 2016 23. pii: S0167-5273.

33. Corrà U, Agostoni P, Giordano A, *et al*. The metabolic exercise test data combined with Cardiac And Kidney Indexes (MECKI) score and prognosis in heart failure. A validation study. *Int J Cardiol* 2016; 203:1067-72.

34. Murphy RM, Shah RV, Malhotra R, *et al*. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. *Circulation* 2011; 124:1442-51.

35. Olson LJ, Arruda-Olson AM, Somers VK, Scott CG, Johnson BD. Exercise oscillatory ventilation: instability of breathing control associated with advanced heart failure. *Chest* 2008; 133:474-81.

36. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J* 2007; 153:859-67.

37. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J* 2008;, 29:2751-9.

38. Arena R, Myers J, Aslam SS, *et al*. Peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope in patients with heart

failure: A prognostic comparison. *Am Heart J* 2004; 147:354–60.
39. 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.
40. Palange P, Ward SA, Carlsen KH, *et al*. Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29:185-209. 123.
41. Cahalin LP, Arena R. Breathing exercises and inspiratory muscle training in heart failure. *Heart Fail Clin* 2015; 11:149-72.
42. McParland C, Krishnan B, Wang Y, Gallagher CG. Inspiratory muscle weakness and dyspnea in congestive heart failure. *Am Rev Respir Dis* 1992; 146:467-72.
43. Walsh JT, Andrews R, Johnson P, Phillips L, Cowley AJ, Kinnear WJ Inspiratory muscle endurance in patients with chronic heart failure. *Heart* 1996; 76:332-6.
44. Mancini DM, Henson D, LaManca J, Levine S. Evidence of reduced respiratory muscle endurance in patients with heart failure. *J Am Coll Cardiol* 1994; 24:972-81.
45. Meyer FJ, Zugck C, Haas M, *et al*. Inefficient ventilation and reduced respiratory muscle capacity in congestive heart failure. *Basic Res Cardio*l 2000; 95:333-42.
46. Meyer FJ, Borst MM, Zugck C, *et al.* Respiratory muscle dysfunction in congestive heart failure-clinical correlation and prognostic significance. *Circulation* 200; 103:2153-8.
47. Daganou M, Dimopoulou I, Alivizatos PA, Tzelepis GE. Pulmonary function and respiratory muscle strength in chronic heart failure: comparison between ischaemic and idiopathic dilated cardiomyopathy. *Heart* 1999; 81:618-20.
48. McIntosh RA, Silberbauer J, Veasey RA, *et al*. Tissue Doppler-derived contractile reserve is a simple and strong predictor of cardiopulmonary exercise performance across a range of cardiac diseases. *Echocardiography* 2013; 30:527-33.
49. Okumura T Hirashiki A, Yamada S, *et al*. Association between cardiopulmonary exercise and dobutamine stress testing in ambulatory patients with idiopathic dilated cardiomyopathy: a comparison with peak VO_2 and VE/VCO_2 slope. *Int J Cardiol* 2013; 162:234-9.
50. Parthenakis F, Patrianakos A, Nyktari E. Prognostic value of NT-pro BNP, left ventricular inotropic reserve and cardiopulmonary exercise test in patients with non-ischemic dilated cardiomyopathy *Int J Cardiol* 2011; 147:326-8.
51. Myers J, Ashley E. Dangerous curves: a perspective on exercise, lactate, and the anaerobic threshold. *Chest* 1997; 111:787-95.
52. Myers J, Principles of exercise prescription for patients with chronic heart failure. *Heart Fail Rev* 2008; 13:61-8.
53. Liu YL, Sun XG, Gao H, Zhang ZY, Feng J, Jiang LQ, Zhang J, Xi JN, Zhou JM, Ge WG. [Preliminary report of using cardiopulmonary exercise testing. guide exercise rehabilitation in patients with chronic heart failure.] *Zhongguo Ying Yong Sheng Li Xue Za Zhi.* 2015; 31:374-7. (Chinese)
54. Lewis GD, Shah RV, Pappagianopolas PP, *et al*. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. *Circ Heart Fail* 2008; 1:227-33.
55. Moore B, Brubaker PH, Stewart KP, Kitzman DW. $\dot{V}E/\dot{V}CO2$ slope in older heart failure patients with normal versus reduced ejection fraction compared with age- matched healthy controls. *J Card Fail* 2007; 13:259-62.
56. Witte KK, Nikitin NP, Cleland JG, Clark, AL. Excessive breathlessness in patients with diastolic heart failure. *Heart* 2006; 92:1425-9.
57. Guazzi M, Myers J, Peberdy MA. Cardiopulmonary exercise testing variables reflect the degree of diastolic dysfunction in patients with heart failure normal ejection fraction. *J Cardiopulm Rehabil Prev* 2010; 30: 165-72.
58. Guazzi M, Arena R, Halle M, *et al* 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circ* 2016; 133: e694-e711.