Breathing Intolerance Index and Control of Ventilation, a Non-invasive Method for Evaluating Inspiratory Muscle Endurance at Rest and Exercise, in Patients with Cardiomyopathy: One Year Follow-up

Kavitha Bagavathy¹, Michael Fong², Luanda Grazette², Zhanghua Chen³ and Ahmet Baydur¹

¹Division of Pulmonary, Critical Care and Sleep Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA
²Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA
³Department of Preventive Medicine, Division of Biostatistics, Keck School of Medicine, University of Southern California, Los Angeles, USA

Abstract

Rationale: Inspiratory muscle endurance as expressed by the tension-time index of the diaphragm [TTI=(Pdi/Pdimax) × (T/Ttot)] in normal subjects and cardiorespiratory disorders requires the use of esophageal and gastric balloons. A noninvasive technique can be used in which the ratio of tidal volume to vital capacity (VT/VVC) is substituted for Pdi/Pdimax, with the resulting relationship [(T/Ttot) × (VT/VVC)] called the breathing intolerance index (BIT). The response to medical management of BIT in patients with cardiomyopathy with chronic heart failure has not been assessed before and after medical management.

Objectives: To compare control of ventilation and BIT in patients with stable dilated cardiomyopathy at rest and exercise, and to analyze BIT, oxygen uptake and carbon dioxide elimination at baseline and approximately one year after initiating medical management.

Methods: Control of ventilation and BIT were assessed in 24 patients (mean age 55.5 years; 17 males) at rest and at peak exercise during bicycle ergometry, at baseline and approximately 14 months later.

Results: Median peak VO₂ was 12.9 mL/kg/min and 14.3 mL/kg/min at baseline and followup, respectively (p<0.036, adjusted for age, gender and BMI). It increased 4.3 times from rest to peak exercise at baseline and 4.7 times at followup (NS). Peak VO₂ increased by 10.5% between baseline and followup (p=0.036 after adjusting for age, sex and BMI). BIT did not change significantly. Peak VO₂/BIT increased significantly from baseline to follow-up (p=0.008, adjusted for age, sex and BMI). No patients died or experienced acute heart failure during the study.

Conclusions: Peak VO₂ in relation to non-invasively measured peak tension-time index of the respiratory muscles (BIT) increases significantly after one year of medical management, indicating increased efficient oxygen utilization as cardiac function improves. BIT is useful for noninvasively assessing inspiratory muscle endurance and relating oxygen uptake to ventilation in patients with dilated cardiomyopathy and chronic congestive heart failure.

Keywords: Breathing intolerance index; Exercise; Cardiomyopathy; Control of ventilation

Abbreviations: ANOVA: Analysis of Variance; BIT index: Breathing Intolerance Index; FEV₁: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; MVV: Maximum Voluntary Ventilation; Vₑ: Tidal Volume; Tᵢ: Inspiratory Time; Tₑ: Expiratory Time; TTINDEX: Tension-Time Index of the Diaphragm; TTmus: Tension-Time Index of Inspiratory Muscles; V’: Minute Ventilation; V’O₂: Oxygen Uptake; V’CO₂: Carbon Dioxide Elimination

Introduction

Exercise intolerance due to dyspnea and fatigue is a frequent and disabling symptom in patients with congestive heart failure. Skeletal muscle weakness and reduced respiratory muscle endurance contribute to these symptoms [1-4]. The current New York Heart Association (NYHA) classification of patients according to exercise limitation is a subjective measure of disability and has limited relation to objective measures of exercise tolerance. The tension-time index of the diaphragm [TTINDEX] is the product of the ratio of the mean transdiaphragmatic pressure swing divided by the maximum transdiaphragmatic pressure (Pdi/Pdimax) and the inspiratory time divided by the total breath time (Ti/Ttot) and is related to diaphragm endurance. A noninvasive technique employed by Koga et al. [6] in which the ratio of tidal volume to vital capacity (VT/VVC) was substituted for Pdi/Pdimax, with the resulting relationship [(T/Ttot) × (VT/VVC)] called the breathing intolerance index (BIT). Koga and associates [6] applied the BIT index to predict the need for noninvasive ventilation in patients with bronchial asthma and restrictive thoracic/neuromuscular disorders. Later, Baydur and Chen [7] demonstrated that resting BIT was significantly greater in COPD and obese patients than in control subjects and even higher in seated position in both cohorts primarily due to an increase in VT in this position.

The tension-time index of the diaphragm is markedly increased in patients with chronic heart failure in contrast to healthy subjects [8], approaching levels shown to generate fatigue, as demonstrated

*Corresponding author: Ahmet Baydur, Division of Pulmonary, Critical Care and Sleep Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA, Tel: 3234097184; Fax: 3232267238; E-mail: baydur@usc.edu

Received December 21, 2017; Accepted December 26, 2017; Published December 29, 2017

Citation: Bagavathy K, Fong M, Grazette L, Chen Z, Baydur A (2017) Breathing Intolerance Index and Control of Ventilation, a Non-invasive Method for Evaluating Inspiratory Muscle Endurance at Rest and Exercise, in Patients with Cardiomyopathy. One Year Follow-up. J Pulm Respir Med 7: 440. doi: 10.4172/2161-105X.1000440

Copyright: © 2017 Bagavathy K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
by Bellemare and Grassino [5]. In 2016, our group [9] found that in patients with cardiomyopathy, resting BIT was 50% higher than in healthy control subjects. Even though there was a threefold increase in BIT in these patients at peak exercise, the difference in BIT at peak exercise was not statistically significant between cohorts, suggesting that respiratory muscle endurance was not compromised in the cardiomyopathy patients.

The purpose of this study was to compare indices of control of ventilation and BIT in patients with stable dilated cardiomyopathy during rest and exercise, at baseline, and at approximately one year after initiating medical management, and to analyze the relation of BIT to oxygen uptake at rest and peak exercise (V\text{O} \text{, max}). A secondary objective was to determine if an increase in BIT in relation to V\text{O} \text{, could predict the occurrence of respiratory impairment related to heart failure.

**Methods**

**Subjects**

Clinically stable subjects with dilated cardiomyopathy were retrospectively evaluated after undergoing two cardiopulmonary exercise tests approximately one year apart. Testing was recommended by their primary cardiologist for evaluation of exercise tolerance and response to medical therapy. All patients were in clinically stable condition with no worsening of heart failure or change of cardiac medications in the 2 months prior to the tests. All patients were receiving medical management of their cardiomyopathy in accordance with the 2013 American College of Cardiology Foundation/American Heart association (ACCF/AHA) guidelines for management of heart failure [10,11]. Patients were recorded receiving the following medications: Beta-blockers (n=18), loop diuretics (16), spironolactone (18), torsemide (1), digoxin (7), angiotensin receptor antagonists (9), angiotensin converting enzyme inhibitors (7), vasodilators (7) and amiodarone (2). History concerning medical and smoking history and respiratory symptoms, as well as hospitalizations for acute cardiorespiratory illness were recorded. Patients with asthma, primary restrictive respiratory disorders and acute cardiorespiratory illnesses were excluded. The study was approved by the Institutional Review Board (HS-14-00244). Findings of this study were reported previously in part as an abstract [12].

**Pulmonary function testing**

Spirometry was performed while seated with a Collins GS/PLUS or DSII/PLUS System (Warren Collins; Braintree, MA, or Ultima PF, MedGraphics, Saint Paul, MN). The cut-off point of FEV\text{1}/FVC for COPD was 0.7 [13]. Predicted values for post-bronchodilator FEV\text{1}, FVC and FEV\text{1}/FVC were from Schoenberg et al. [14].

**Exercise testing and control of ventilation**

Subjects refrained from eating or drinking coffee for at least 12 hours before testing. They breathed room air through the equipment assembly with a nose clip on. The exercise test was performed on a calibrated bicycle ergometer (Lode, Amsterdam, Netherlands). Subjects wore a noseclip and breathed through a low resistance (1.5 cm H\text{2}O/L/s) and low dead space (45 mL) breathing valve. The valve was connected by the expiratory circuit to a breath-by-breath automated exercise metabolic system (Ultima CardiO2, MedGraphics, St. Paul, Minnesota). Flow was measured with a heated bidirectional Pitot tube flow sensor and differential pressure transducer (MedGraphics) that was linear over the experimental range of flow up to 14 L/s. Volume was obtained by integration of digitized flow. A closed system ensured that end-expiratory volume remained constant. Each subject underwent a 3-minute trial run in order to become accustomed to the procedure. Subjects were monitored for leaks at the mouthpiece. Exercise testing consisted of acquiring multiple measurements during 3 minutes of rest, 3 minutes of unloaded cycling, followed by progressively increasing work by 10 Watts/minute to maximum tolerance. At each stage, control of ventilation data were obtained from the last 5 to 10 breaths of steady state ventilation. The system continuously measured oxygen uptake, carbon dioxide output, and respiratory exchange ratio. Before each test, the gas analyzers were calibrated with two gas mixtures of known oxygen and carbon dioxide concentration. Heart rate was continuously recorded on a cardioscope and electrocardiogram was periodically recorded.

**Statistics**

Medians, 25\text{th} and 75\text{th} percentiles are presented in the table to describe the distribution of characteristics and lung function measures of 24 participants at baseline and follow-up visit after treatment. Wilcoxon signed rank test was used to assess differences in physiologic variables between rest and peak exercise status [15]. Because of the small sample size and the data exhibited skewed distributions for many of the lung function variables, characteristics and measures of lung function tests were transformed using Blom normal scores for nonparametric data analysis. Individual characteristics and measures of lung function tests were compared before and after treatment using mixed effects model [16-18] to allow a random intercept for each individual and to control for within-individual correlations among repeated measures. Age, sex and BMI are adjusted for in the model for their potential confounding effect. All statistical tests were two-sided at a 0.05 significance level. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for data analysis.

**Results**

**Anthropometric data and baseline characteristics**

Control of ventilation and respiratory muscle endurance were analyzed in 24 subjects with dilated cardiomyopathy (15 ischemic and 9 non-ischemic). There were 17 male and 7 female patients. Mean age at baseline and at follow up was 55.5 and 57.0 years, respectively. Baseline BMI was 28.4 kg/m\text{2} with no significant change on follow up. Mean (± SD) baseline and followup estimated left ventricular ejection fraction (LVEF) by transthoracic echocardiography was 34.4 ± 11.1 and 38.1 ± 11.9, respectively (p<0.05). Mean follow up time was 14.3 months.

**Spirometric and control of ventilation data**

Table 1 shows that, from baseline to followup, forced vital capacity (FVC) and maximum voluntary ventilation (MVV) increased by 3.6% (p=0.015), adjusted for age, gender and BMI and 2.1% (p=0.03), respectively, without significant changes in FEV\text{1}, FVC and FEV\text{1}/FVC. Indices for control of ventilation changed significantly from rest to peak exercise, with VT increasing by 2.6- and 2.5-fold at baseline and followup, respectively, and the Ti decreasing by 32% on both occasions (p<0.01), T\text{c} diminished by 46% and 50% respectively (both p<0.01), while Ti/T\text{c} increased by 29% and 37%, respectively (both p<0.001). The ratio of tidal volume to FVC increased by 2.8- and 2.9-fold from baseline to followup, respectively (both p<0.001). These changes were not significant between baseline and followup. From rest to peak exercise, BIT increased by 3.8- and 3.7-fold at baseline and followup, respectively (both p<0.0001), reflecting the marked increase in VT.
At followup, compared to baseline, the relative increase in \( V'O_2 / B IT \) of oxygen uptake in relation to ventilatory effort, increased by 26% from exercise on follow up (\( p=0.008 \)), while the \( V'CO_2 / B IT \) relationship at rest decreased by 14% at followup, but increased by 21% at peak exercise (\( p=0.033 \)). Resting \( O_2 \)-pulse did not increase.

Exercise data

When adjusted for age, sex and BMI, median peak \( V'O_2 \) increased by 10.5% (1.35 ml/kg/min) over the study period (\( p=0.036 \)), although resting \( V'O_2 \) did not change significantly. At baseline, \( V'O_2 \) increased by 4.3 times at peak exercise while it increased 4.7-fold at followup. The \( O_2 \)-pulse (reflecting stroke volume) at peak exercise, increased by 14% (\( p=0.033 \)) at followup; resting \( O_2 \)-pulse did not increase. Compared to baseline, the BIT index trended towards decreasing values, both at AT and peak exercise, but differences were not statistically significant (Table 1 and Figure 1A). At baseline, the \( V'O_2 / B IT \) ratio, an expression of oxygen uptake in relation to ventilatory effort, increased by 26% from rest to anaerobic threshold, then decreased by 18% at peak exercise. At followup, compared to baseline, the relative increase in \( V'O_2 / B IT \) from rest to anaerobic threshold nearly doubled (54%, \( p<0.02 \)) but decreased by only 6% at peak exercise. The baseline \( V'O_2 / B IT \) ratio at rest decreased by 14% at followup, but increased by 21% at peak exercise on follow up (\( p=0.008 \)), while the \( V'CO_2 / B IT \) relationship increased by 10% and 25%, respectively, at anaerobic threshold and peak exercise. No patients experienced any episodes of acute heart failure or died during the study period. Figure 1B shows, in graphical form, the changes in the components of the BIT index and relationship of \( V'O_2 \) to BIT from baseline to followup. As reflected in Table 1, while \( Vt/VC \) and \( V'O_2 / B IT \) sharply increased from resting to peak exercise both at baseline and followup, there were no significant differences between the time points. No patients experienced acute heart failure or died during the study period.

Discussion

To our knowledge this study is the first to evaluate control of ventilation and inspiratory muscle effort using a noninvasive method (i.e., without using the esophageal balloon method) in patients with dilated cardiomyopathy under resting and exercise conditions approximately one year apart. The main findings of this study were that: (1) peak \( V'O_2 \) increased significantly after approximately one year of medical management, (2) BIT index did not change significantly over the same period, and (3) patients did not exhibit inspiratory muscle fatigue during exercise, a finding that did not change at followup.
Control of ventilation and breathing intolerance index

We assessed the impact of chronic heart failure on respiratory muscle endurance, at rest and peak exercise and its response to medical management at one year by assessing changes in control of ventilation. At rest, the ventilatory pattern (VT, T1, TW, V'CO2, V'TOT) observed in our cardiomyopathy patients was similar to that in patients with chronic heart failure reported by other investigators [19-21]. Koga et al. [6] found that during resting breathing, BIT index was, on average, 0.186 in patients with asthma and restrictive thoracic disorders requiring nocturnal noninvasive positive-pressure ventilation, significantly greater than those of the neuromuscular and asthma patients reported by Koga et al. [6]. During resting breathing, BIT becomes useful as a predictor for respiratory failure when its value increases above stable resting conditions, an event that did not occur in our patients.

Oxygen uptake and exercise capacity

The peak VO2 after 1 year of medical management (14.3 ml/kg/min) was comparable to that of 67 patients with hypertrophic cardiomyopathy undergoing 16 weeks of a moderate-intensity training program reported by Saberi et al. (21.3 ml/kg/min) [21]. These authors reported an increase in peak VO2 amounting to 1.35 ml/kg/min, or 6.4% of the baseline value, similar to the increase (amounting to 10.5%) we found. Patients with chronic (stable) heart failure exhibit decreased maximal exercise capacity and slower transitions to and from submaximal levels of exercise [22-24]. Peak VO2 is a reliable indicator of prognosis in heart failure (but recently has been superseded by the slope of V'CO2/V'TOT, and relates to cardiac output and muscle perfusion [25]. Exercise limitation is further exacerbated by down regulation of beta-receptors and increased pulmonary vascular resistance [26]. Moreover, pulmonary edema reduces lung volume [27] and compliance, further increasing the work of breathing.

Relation between ventilation variables and oxygen uptake and carbon dioxide production

The VO2-BIT relationship describes oxygen uptake for a given degree of ventilatory effort, and offers the advantage of not having to use the esophageal balloon technique to directly measure the work produced by the respiratory muscles. We found that both at baseline and followup, VO2/BIT increased from rest to anaerobic threshold and then decreased slightly at peak exercise. Compared to baseline, the relative increase in VO2/BIT from rest to anaerobic threshold was more prominent at followup, indicating more efficient oxygen utilization after treatment. Our findings of the changes in the VO2/BIT relationship are analogous to those of Sun et al. [28] who described changes in VO2/V'CO2 (referred to as the oxygen uptake efficiency, OUE) from rest to peak exercise in normal subjects and subjects with 3 different severities of heart failure. In all their patients, OUE increased rapidly and reached a plateau (OUEP) just before the anaerobic threshold and then diminished until exercise ended (Figure 1) [28]. In patients with very severe heart failure, the mean OUEP was 52% of that of normal subjects. They determined that OUEP was the strongest predictor of early mortality. We previously reported that median peak VO2 for patients with chronic heart failure was 54% lower than in control subjects [9], similar to findings by Sietsema et al. [22] who showed that peak VO2 (corrected for weight) was 62% lower than in normal control subjects. Since BIT was not significantly different between normal control subjects and those with heart failure, median VO2/BIT was 46% that of healthy controls, similar to changes in VO2/V'TOT described by Sun et al. [28]. Furthermore, our finding of an increase in the peak VO2/BIT after one year was almost entirely due to increase in the O2 uptake, as BIT did not change significantly. Given that BIT is analogous to V'TOT, a rising V'CO2/BIT during exercise (analogous to a decrease in the slope of V'CO2/V'TOT) should be associated with a reasonably good prognosis in chronic heart failure. The increase in the ratio indicates that lung perfusion (that is, cardiac output) increases with respect to ventilation, commensurate with increase in metabolic demand and the need to eliminate CO2. Indeed, none of our patients experienced acute decompensation or died during the period of study, despite borderline values of VO2 max. In an earlier study, we found that in patients with chronic heart failure resting V'TOT was higher than in healthy control subjects [9], as have others [28]. V'TOT, however, increased by only as half as much as it did in control subjects at peak exercise [9], reflecting decreased strength and endurance of respiratory muscles. In addition, low end-tidal PaCO2 and elevated dead space to tidal volume ratio (Vd/Vt) have been shown to be strong predictors of...
mortality since a low peak PaCO₂ for a given level of exercise produces an increase in the V̇O₂/V̇CO₂ slope, a strong prognostic indicator [29].

Limitations

There were some limitations to this study, the first being its retrospective design. Being a single center study, findings and conclusions may also limit generalizability. However, patients were selected for analysis based on strict diagnostic criteria obtained from medical records. Principles of testing and data analysis followed standard practice. Inclusion criteria were strictly maintained. Second, we did not assess for periodic (oscillatory) breathing (PB) during cardiopulmonary testing. Periodic breathing has been associated with much more severe disease and poor prognosis in heart failure [30,31]. Future studies may also focus on this aspect of control of ventilation and its influence on respiratory muscle function.

Conclusions

The BIT index is useful for evaluating respiratory muscle endurance under resting and exercise conditions in patients with cardiomyopathies. V̇O₂ and V̇O₂/BIT increase significantly at peak exercise from baseline under resting and exercise conditions in patients with cardiomyopathies. Periodic breathing has been associated with much more severe disease and poor prognosis in heart failure [30,31]. Future studies may also focus on this aspect of control of ventilation and its influence on respiratory muscle function.

Acknowledgements

The authors thank Dr. Amy Tran and Dr. Leejo Pallickal for assisting in collecting patient data.

References

1. Ambrosino N, Opasich C, Crotti P, Cobelli F, Tavazzi L, et al. (1994) Breathing pattern, ventilatory drive and respiratory muscle strength in patients with chronic heart failure. Eur Respir J 7: 17-22.
2. Hammond MD, Bauer KA, Sharp JT, Rocha RD (1990) Respiratory muscle strength in congestive heart failure. Chest 98: 1091-1094.
3. McParland C, Krishnan B, Wang Y, Gallagher CG (1992) Inspiratory muscle weakness and dyspnea in chronic heart failure. Am Rev Respir Dis 146: 467-472.
4. Mancini DM, Ferraro N, Nazzaro D, Chance B, Wilson JR (1991) Respiratory muscle deoxygenation during exercise in patients with heart failure demonstrated with near-infrared spectroscopy. J Am Coll Cardiol 18: 492-498.
5. Bellemare F, Grassino A (1982) Effect of pressure and timing of contraction on human diaphragm fatigue. J Appl Physiol Respir Environ Exerc Physiol 53: 1190-1195.
6. Koga T, Watanabe K, Sano M, Ishikawa Y, Bach JR (2006) Breathing intolerance index: A new indicator for ventilator use. Am J Phys Med Rehabil 85: 24-30.
7. Baydur A, Chen Z (2013) Breathing intolerance index in COPD and obesity: A comparative observational study. Open J Respir Dis 3: 119-127.
8. Mancini DM, Henson D, LaManca J, Levine S (1992) Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. Circulation 86: 909-918.
9. Baydur A, Tran A, Pallickal L, Fong M, Grazette L, et al. (2016) Breathing intolerance index (BIT) and its relation to exercise data: Noninvasive assessment of inspiratory muscle endurance during rest and exercise in patients with chronic obstructive pulmonary disease and cardiovascular disorders. Chr Obstruct Pulmon Dis 1: 11.
10. Richardson P, McKenna W, Bristow M (1996) Report of the 1995 world health organization/international society and federation of cardiology task force on the definition and classification of cardiomyopathies. Circulation 93: 841-842.
11. Hunt SA, Abraham WT, Chin MH (2005) American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society: ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure); Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 112: e154-e235.
12. Bagavathy K, Tran A, Pallickal L, Fong M, Baydur A (2016) Breathing intolerance index (BIT) in cardiomyopathy patients - understanding respiratory muscle endurance in response to exercise with medical management. Am J Respir Crit Care Med 193: A5643.
13. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F (2005) Interpretative strategies for lung function tests. Eur Respir J 26: 948-968.
14. Schoenberg JB, Beck GJ, Bouhuys A (1978) Growth and decay of pulmonary function in healthy blacks and whites. Respir Physiol 33: 367-393.
15. Wilcoxon F (1945) Individual comparisons by ranking methods. Biometrics Bulletin 1: 80-83.
16. Blom G (1958) Statistical estimates and transformed beta-variables. John Wiley & Sons, New York, USA.
17. Fisher RA (1918) The correlation between relatives on the supposition of mendelian inheritance. Transactions of the Royal Society of Edinburgh 52: 393-444.
18. Harris CR (1975) Best linear unbiased estimation and prediction under a selection model. Biometrics 31: 423-447.
19. Al-Rawas OA, Carter R, Richens D, Stevenson RD, Naik SK, et al. (1995) Ventilatory and gas exchange abnormalities on exercise in chronic heart failure. Eur Respir J 8: 201-207.
20. Vibareli N, Hayot M, Pellicc PM, Corret J, Ramonatxo AM, et al. (1998) Non-invasive assessment of inspiratory muscle performance during exercise in patients with chronic heart failure. Eur Heart J 19: 766-773.
21. Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal P, et al. (2017) Effect of moderate intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy. A randomized clinical trial. JAMA 317: 1349-1357.
22. Sietsema KE, Ben-Dov I, Zhang YY, Sullivan C, Wasserman K (1994) Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. Chest 105: 1693-1700.
23. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, et al. (2010) Clinician’s guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. Circulation 122: 225-225.
24. Stringer WW, Hansen JE, Wasserman K (1997) Cardiac output estimated noninvasively from oxygen uptake during exercise. J Appl Physiol 82: 908-912.
25. Harrington D, Anker SD, Chua TP, Webb-Peploe KM, Ponikowski P, et al. (1997) Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. J Am Coll Cardiol 30: 1758-1764.
26. Butler J, Chomsky DB, Wilson JR (1999) Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol 34: 1802-1806.
27. Light RW, George RB (1983) Serial pulmonary function in patients with acute heart failure. Arch Intern Med 143: 429-433.
28. Sun XG, Hansen JE, Stringer WW (2012) Oxygen uptake efficiency plateau best predicts early death in heart failure. Chest 141: 1284-1294.
29. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD (2007) Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: An unfavorable combination. Am Heart J 153: 859-867.
30. Wasserman K (2010) Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Card 55: 1814-1823.
31. Corra U, Giordano A, Bosimini E (2002) Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest 121: 1572-1580.