Relationship Between Respiratory Compensation Point and Anaerobic Threshold in Patients With Heart Failure With Reduced Ejection Fraction

Taisuke Nakade, MD; Hitoshi Adachi, MD; Makoto Murata, MD; Shigeto Naito, MD

Background: Cardiopulmonary exercise testing (CPX) is used in the prognostic evaluation of patients with heart failure with reduced ejection fraction (HFrEF). In these patients, the ventilation feedback system is dysfunctional, and overactive peripheral chemoreceptors may be responsible for the early appearance of the respiratory compensation point (RCP) after the anaerobic threshold (AT). The mechanism of RCP appearance remains unknown and very few studies have reported the relationship between RCP and heart failure. We hypothesized that the duration between the RCP and AT (RCP-AT time) can predict the severity of cardiac disorders and prognosis in patients with HFrEF.

Methods and Results: We enrolled 143 patients with HFrEF who underwent symptom-limited maximal CPX between 2012 and 2016. During a median follow-up of 1.4 years, cardiovascular death occurred in 45 participants (31%). The patients who died had a significantly shorter RCP-AT time and lower hemoglobin (Hb) levels than those who survived (P<0.001 and P=0.01, respectively). Cox regression analyses revealed RCP-AT time and Hb level to be independent predictors of cardiovascular death in patients with HFrEF (P<0.001 and P=0.018, respectively).

Conclusions: RCP-AT time can better predict prognosis in patients with HFrEF than the magnitude of increase in oxygen consumption within the isocapnic buffering domain (∆V˙ O2 AT-RCP). It may be useful as a new prognostic indicator in these patients.

Key Words: Anaerobic threshold; Cardiopulmonary exercise testing; Exercise tolerance; Heart failure with reduced ejection fraction; Respiratory compensation point
in chronic HF patients, the RCP-AT time could be useful in estimating the rate of aerobic and anaerobic metabolism after AT and could be related to the severity of HFrEF. However, they did not identify the exact relationship between RCP-AT time and prognosis in patients with HF.

In patients with HF, the feedback system that controls ventilation is dysfunctional because of an increase in the controller gain (increased sensitivity to changes in arterial O₂ and CO₂ levels), reduction in system damping (decrease in total body stores of O₂ and CO₂), and a delay in information transfer (circulation time between the lungs and brain). The increased chemoreceptor drive may represent the high controller gain, whereby small changes in arterial O₂ and CO₂ levels can result in inappropriately large alterations of the system output. Therefore, over-active peripheral chemoreceptors may be responsible for the early appearance of the RCP after AT. Based on the understanding of this mechanism and results of past studies, we hypothesized that patients with severe HF have an inappropriate feedback system and that RCP appears earlier after AT; in other words, the shorter RCP-AT time in patients with HFrEF could indicate poor prognosis.

In this study, we evaluated the relationship between RCP-AT time and prognosis in patients with HFrEF. We analyzed and compared several previously reported prognostic risk factors, including Na, eGFR, % peak VO₂, VE vs. VCO₂ slope, EF, and B-type natriuretic peptide (BNP).

**Methods**

**Patient Selection**

The study cohort was retrieved from the Gunma Prefectural Cardiovascular Centre Database, established in 2012 for patients who newly visited the hospital. Data for patients who underwent symptom-limited maximal CPX between 2012 and 2016 were analyzed. The inclusion criteria were previous or present HF symptoms (New York Heart Association [NYHA] functional classes II–III), American College of Cardiology/American Heart Association [ACC/AHA] classification stage C), previous or present HF symptoms (New York Heart Association [NYHA] functional classes II–III, and those who died during the follow-up period included cardiovascular death, and the area under the curve (AUC) was expressed as V̇O₂ at the highest WR. AT was measured using the V-slope method.

The patients included in this study were those who underwent symptom-limited CPX on an upright cycle ergometer (StrengthErgo8; Mitsubishi Electric Engineering, Tokyo, Japan) with an ECG machine (ML-9000, Fukuda Denshi, Ltd., Tokyo, Japan). CPX was performed 2–4 h after a light meal. The tests included, as per the recommendations of Buchfuhrer et al., 3 min of rest and a 3-min warm-up at 0watt, followed by a continuous increase in the work rate (WR) by 1 W every 6s until exhaustion. The criteria for halting the exercise testing in this study are outlined in the American College of Sports Medicine guidelines. The increments in WR levels were chosen on the basis of the ability of the patient to perform the exercises within 8–15 min. We measured oxygen consumption (VO₂), carbon dioxide production (VCO₂), and minute ventilation (VE) on a breath-by-breath basis using a gas analyzer (MINATO 300S, Minato Science Co., Ltd., Osaka, Japan). Peak VO₂ was determined as VO₂ at the highest WR. AT was measured using the V-slope method.

In this study, we evaluated the relationship between RCP-AT time and prognosis in patients with HFrEF. We analyzed and compared several previously reported prognostic risk factors, including Na, eGFR, % peak VO₂, VE vs. VCO₂ slope, EF, and B-type natriuretic peptide (BNP). The time interval from the date of CPX to cardiovascular death, and the area under the curve (AUC) was expressed as V̇O₂ at the highest WR. AT was measured using the V-slope method.

The patients included in this study were those who underwent symptom-limited CPX on an upright cycle ergometer (StrengthErgo8; Mitsubishi Electric Engineering, Tokyo, Japan) with an ECG machine (ML-9000, Fukuda Denshi, Ltd., Tokyo, Japan). CPX was performed 2–4 h after a light meal. The tests included, as per the recommendations of Buchfuhrer et al., 3 min of rest and a 3-min warm-up at 0watt, followed by a continuous increase in the work rate (WR) by 1 W every 6s until exhaustion. The criteria for halting the exercise testing in this study are outlined in the American College of Sports Medicine guidelines. The increments in WR levels were chosen on the basis of the ability of the patient to perform the exercises within 8–15 min. We measured oxygen consumption (VO₂), carbon dioxide production (VCO₂), and minute ventilation (VE) on a breath-by-breath basis using a gas analyzer (MINATO 300S, Minato Science Co., Ltd., Osaka, Japan). Peak VO₂ was determined as VO₂ at the highest WR. AT was measured using the V-slope method.

The parameters compared between those who survived and those who died during the follow-up period included basic demographic data, such as age, and body mass index (BMI); cardiovascular risk factors, such as number of lymphocytes, Hb, Na, UA, and total cholesterol levels; biomarkers, such as BNP levels; and CPX parameters, such as RCP-AT time, VO₂, AT, peak VO₂, VE vs. VCO₂ slope, load, PETCO₂, and peak O₂ pulse. The distribution of each continuous variable was tested for normality using the Shapiro-Wilk test, and the results are expressed as mean ± standard deviation. Variables with a skewed distribution are expressed as median [interquartile range]. Statistical analyses were performed using unpaired t-test or Mann-Whitney test for continuous variables and the chi-square test for categorical variables. To investigate the association with cardiovascular death, univariate and multivariate Cox regression analyses were applied to examine the aforementioned potential factors, including Na, eGFR, % peak VO₂, VE vs. VCO₂ slope, EF and BNP. We did not use peak heart rate, nadir VE/VCO₂, or peak load in the multivariate analyses, even though there was a significant difference between the 2 groups, because we chose our explanatory variables based on experience in specialized fields and the previous literature. Receiver-operating characteristic (ROC) curves were used to identify the sensitivity and specificity of RCP-AT time for predicting cardiovascular death, and the area under the curve (AUC)
was calculated. Survival analyses using Kaplan-Meier models were also performed. These analyses were performed using the Statistical Package for Social Sciences 21.0J for Mac (IBM Corp., Armonk, NY, USA). Statistical significance was set at a two-sided P value <0.05.

Ethical Statement
This study was approved by the Ethics Committee of Gunma Prefectural Cardiovascular Centre (approval no.: 31009) and was conducted in accordance with the Declaration of Helsinki. Each patient gave informed consent.

Results
Baseline Clinical Characteristics of Patients
Table 1 summarizes the baseline characteristics of the participants who survived and those who died from cardiovascular death during a median follow-up period of 1.4 years. Cardiovascular death occurred in 45 participants (31%): 33 (23%) died of HF, and 12 (8%) from sudden death caused by arrhythmia. The mean age and BMI were not significantly different between groups. The participants who died had lower Hb and higher BNP levels (12.9±1.5 g/dL vs. 14.2±3.1 g/dL, P=0.01; and 249.0 [198.0, 629.7] pg/mL vs. 164.9 [106.9, 160.3 mL/min, P=0.01, respectively).

Comparison of CPX Parameters
The CPX parameters of each group are summarized in Table 2. There were no significant differences in systolic blood pressure at rest and peak, or in heart rate at peak exercise during CPX. In contrast, the heart rate at rest was significantly higher in the patients who died vs. those who survived (78.1±14.2 beats/min vs. 72.1±12.9 beats/min, P=0.01, respectively). There were no significant differences in V̇O₂ at rest and AT; however, significant differences in RCP V̇O₂ and peak V̇O₂ were observed. Parameters indicating cardiac function during exercise such as V̇E vs. V̇CO₂ slope (27.8 [32.3, 43.2] vs. 33.1 [29.6, 37.0], P=0.006), nadir V̇E/V̇CO₂ (42.1 [36.4, 43.7] vs. 38.6 [32.5, 41.2], P<0.001), maximum PETCO₂ (34.2±4.6 mmHg vs. 38.7±4.3 mmHg, P=0.001), and peak O₂ pulse (7.2 [6.0, 8.9] mL/beats vs. 7.5 [6.0, 9.6] mL/beat, P=0.04) were significantly different between the 2 groups. Finally, RCP-AT time was longer and ∆V̇O₂ AT-RCP was smaller in those who died than in those who survived (99.3±44.0 s vs. 159.5±106.9 s, P<0.001; and 164.9±49.3 mL/min vs. 227.8±160.3 mL/min, P=0.01, respectively).

Table 1. Baseline Characteristics of the Study Patients With HFrEF

| Patient characteristics | Death (n=45) | Survival (n=98) | P value |
|-------------------------|-------------|----------------|---------|
| Sex (M/F)               | 41/4        | 81/17          | 0.85    |
| Age (years)             | 62.2±18.7   | 59.5±14.2      | 0.35    |
| Height (cm)             | 165.9±7.4   | 164.7±7.2      | 0.36    |
| Weight (kg)             | 60.8±13.4   | 64.8±16.3      | 0.18    |
| BMI (kg/m²)             | 22.0±4.2    | 24.8±7.5       | 0.08    |
| LVEF (%)                | 29.3±8.1    | 29.6±15.6      | 0.83    |
| Hb level (g/dL)         | 12.9±1.5    | 14.2±3.1       | 0.01    |
| Lymphocyte count (%)    | 23.4 [18.0, 26.3] | 23.5 [17.5, 29.2] | 0.23 |
| Sodium (mEq/L)          | 140.0 [139.0, 142.0] | 142.0 [138.0, 143.0] | 0.93 |
| Uric acid (mg/dL)       | 6.5±1.2     | 6.8±4.1        | 0.56    |
| Total cholesterol (mg/dL)| 173.0 [146.0, 184.5] | 189.0 [160.0, 234.5] | 0.18 |
| eGFR (mL/min/1.73m²)    | 57.8±30.3   | 62.3±23.5      | 0.47    |
| BNP (pg/mL)             | 249.0 [198.0, 629.7] | 161.4 [106.9, 407.2] | 0.03 |
| NYHA class II/III       | 8/37        | 24/74          | 0.37    |
| Etiology of HF          | Ischemic/non-ischemic | 15/30        | 0.69    |
| Medical history         | Hypertension | 15 (33%) | 31 (31%) | 0.84 |
|                        | Diabetes mellitus | 17 (38%) | 31 (32%) | 0.57 |
| Medical therapy         | β-blockers  | 37 (82%)     | 86 (87%) | 0.43 |
|                        | ACEI/ARB    | 33 (73%)     | 75 (76%) | 0.68 |
|                        | Spironolactone | 21 (47%) | 50 (51%) | 0.71 |

Data are mean±standard deviation, median value [interquartile range], or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BMI, body mass index; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; NYHA, New York Heart Association.
Table 3. Predictors of Cardiovascular Death

| Variable                  | Univariate        | Multivariate       |
|---------------------------|-------------------|--------------------|
| % peak VO<sub>2</sub> (%) | HR 95% CI          | P value            |
|                           | 0.968             | 0.948−0.989        | 0.003              |
| Hb level (g/dL)           | 0.726             | 0.612−0.869        | <0.001             |
| VE vs. VCO<sub>2</sub> slope | 1.023          | 1.002−1.045        | 0.032              |
| Sodium (mEq/L)            | 0.986             | 0.954−1.020        | 0.420              |
| LVEF (%)                  | 0.996             | 0.967−1.028        | 0.825              |
| eGFR (mL/min/1.73 m<sup>2</sup>) | 0.992          | 0.980−1.006        | 0.270              |
| BNP (pg/mL)               | 0.992             | 0.989−1.012        | 0.630              |
| RCP-AT time (s)           | 0.982             | 0.975−0.989        | <0.001             |

| Variable                  | HR 95% CI          | P value            |
|---------------------------|-------------------|--------------------|
| % peak VO<sub>2</sub> (%) | 0.968             | 0.948−0.989        | 0.003              |
| Hb level (g/dL)           | 0.726             | 0.612−0.869        | <0.001             |
| VE vs. VCO<sub>2</sub> slope | 1.023          | 1.002−1.045        | 0.032              |
| Sodium (mEq/L)            | 0.986             | 0.954−1.020        | 0.420              |
| LVEF (%)                  | 0.996             | 0.967−1.028        | 0.825              |
| eGFR (mL/min/1.73 m<sup>2</sup>) | 0.992          | 0.980−1.006        | 0.270              |
| BNP (pg/mL)               | 0.992             | 0.989−1.012        | 0.630              |
| ΔVO<sub>2</sub> AT-RCP (mL/min) | 0.994          | 0.991−0.997        | <0.001             |

Abbreviations as in Tables 1–3.

Table 4. Non-Predictors of Cardiovascular Death

| Variable                  | Univariate        | Multivariate       |
|---------------------------|-------------------|--------------------|
| % peak VO<sub>2</sub> (%) | HR 95% CI          | P value            |
|                           | 0.968             | 0.948−0.989        | 0.003              |
| Hb level (g/dL)           | 0.726             | 0.612−0.869        | <0.001             |
| VE vs. VCO<sub>2</sub> slope | 1.023          | 1.002−1.045        | 0.032              |
| Sodium (mEq/L)            | 0.986             | 0.954−1.020        | 0.420              |
| LVEF (%)                  | 0.996             | 0.967−1.028        | 0.825              |
| eGFR (mL/min/1.73 m<sup>2</sup>) | 0.992          | 0.980−1.006        | 0.270              |
| BNP (pg/mL)               | 0.992             | 0.989−1.012        | 0.630              |
| ΔVO<sub>2</sub> AT-RCP (mL/min) | 0.994          | 0.991−0.997        | <0.001             |

Abbreviations as in Tables 1–3.

Data are mean±standard deviation or median value [interquartile range]. AT, anaerobic threshold; BP, blood pressure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; O<sub>2</sub> pulse, oxygen pulse; Peak VO<sub>2</sub>, oxygen uptake at peak work rate; PETCO<sub>2</sub>, endtidal carbon dioxide pressure; RCP, respiratory compensation point; Rest VO<sub>2</sub>, oxygen uptake at peak work rate; VE, minute ventilation; VCO<sub>2</sub>, carbon dioxide production.
We also performed univariate and multivariate Cox regression analyses that changed the explanatory variables from RCP-AT time to ∆VO₂: AT-RCP. However, ∆VO₂: AT-RCP was not an independent predictor of cardiovascular death (Table 4).

**RCP-AT Time Cutoff Level**

Based on the ROC curve analysis, the optimal cutoff for RCP-AT time to predict cardiovascular death was 127.5 s, with specificity and sensitivity of 63.3% and 77.8%, respectively (AUC=0.762; 95% CI: 0.679–0.845) (Figure 1).

**Long-Term Follow-up and New-Onset Cardiovascular Death**

The event-free survival curve was also evaluated using the RCP-AT cutoff value (127.5 s). Results indicated that individuals with RCP-AT time ≥127.5 s had a significantly higher risk of cardiovascular death than did individuals with RCP-AT time <127.5 s (P<0.001) (Figure 2).

**Discussion**

The present study found that patients with a longer RCP-AT time (127.5 s) had a worse prognosis and greater severity of HF than did patients with shorter RCP-AT time (<127.5 s). Additionally, serum Hb level was an important factor in their prognoses. To the best of our knowledge, this is the first study to investigate the role of RCP-AT time in the prognosis of patients with HFrEF.

During a progressively increasing workload exercise, ventilation follows 3 distinctive domains that are regulated by oxygen uptake, carbon dioxide production, and unbuffered acidosis, respectively.

Ventilation is regulated through a feedback loop between pulmonary gas-exchanging capillaries and chemoreceptors in the carotid bodies (peripheral) or medulla (central). Ventilatory dysfunction may arise from (1) a delay in information transfer (i.e., increased circulation time because of reduced cardiac index), (2) an increase in controller gain, such as increased chemosensitivity to arterial CO₂ and O₂ levels, or (3) a reduction in system damping, such as baroreflex impairment. Abnormal hemodynamic variables are known to be associated with a poor prognosis in conditions of dysfunctional ventilation and the mechanism of augmentation of the chemoreflex may lie in sympathetic overactivity and neurohormonal imbalance, both of which also affect survival in chronic HF. Catecholamines have been shown to increase chemosensitivity, which may further perpetuate the sympathetic drive and contribute to neurohormonal imbalance. The chemoreflex may also be augmented directly because of reduced blood flow to the chemoreceptors — again a reflection of hemodynamic dysfunction. Therefore, the RCP appears early after AT, and patients with shorter RCP-AT time have worse prognosis. A previous study reported that RCP-AT time had a strong correlation with ∆VO₂: ∆Load in patients with chronic HF. Furthermore, increased ∆VO₂: ∆Load suggests high blood flow to the whole body during exercise. Those findings also support our hypothesis.

Carrie et al carried out the first study to test whether the magnitude of increase in VO₂ (ΔVO₂: AT-RCP) within the isocapnic buffering domain predicts syndrome severity and
prognosis in patients with HFrEF. They identified 782 patients with HFrEF and found that ∆VO2: AT-RCP was associated with prognosis in the univariate but not the multivariate analysis. The current study included fewer participants but demonstrated the same results: ∆VO2: AT-RCP was associated with prognosis in patients with HFrEF in the univariate but not the multivariate analysis. This consistency with the previous study validates our findings. Although the mechanism of RCP remains unknown, the definition has been established in many studies. One of the strengths of our study was that we could set the RCP and AT using those definitions. Peak VO2 may depend on the patient’s mental state and can be lower than the actual value because of lack of effort; however, the RCP-AT time is not affected by the patient’s condition, and we could calculate it precisely by the established definitions. By calculating RCP-AT time, we could predict the patient’s prognosis more precisely and evaluate the effect of HFrEF medical treatment and cardiac rehabilitation.

Circulation Journal Vol.84, January 2020

Study Limitations
To the best of our knowledge, this is the first study to investigate RCP-AT time in the prognosis of patients with HF. However, this study has several limitations. First, our sample size was small, and there were few outcomes. Second, this was a retrospective, single-center study, so the possibility of unintentional selection bias cannot be fully excluded. Third, we proved that serum Hb level was an important factor in the prognosis of patients with HFrEF, but the prognostic effect of anemia may differ depending on its cause as well as HF etiology. Unfortunately, we did not investigate the cause of anemia for each HFrEF patient. Linking the cause of anemia and etiology of HF may lead to a more thorough discussion of anemia and the prognosis of HF. Finally, the results of this study are applicable only to patients with HFrEF because patients with preserved systolic function or with other diseases that affect exercise performance were not evaluated.

Conclusions
It is important to perform CPX in patients with HFrEF to assess AT, RCP, and the isocapnic buffering period. However, the RCP-AT time has a wide range and prognostic power, therefore, evaluation of the isocapnic buffering period has physiological significance and prognostic power in patients with HF. We believe that our data will help prove the detailed mechanism of the appearance of RCP. In the future, RCP-AT time may be used to evaluate the therapeutic effects of treatment in patients with HFrEF by comparing the RCP-AT time before and after the treatment.

Acknowledgments
We thank our lecturers Haruyasu Fujita (Gunma University, Department of Public Health, Gunma, Japan) and Lee Bumsuk (Gunma University Graduate School of Health Sciences, Gunma, Japan) for their valuable statistical advice during the preparation of this report. We thank Editage (www.editage.jp) for English language editing.

Author Contributions
T.N. led the study as the principal investigator, prepared the plan for statistical analyses, drafted, and revised the manuscript. H.A. cleaned the data and performed the statistical analyses. M.M. and S.N. collected the data. All authors have approved the final version of the manuscript.

Funding
This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosures
The authors declare that there are no conflicts of interest.

Sources of Support
No support was received to perform the study or for the preparation of the manuscript.

References
1. Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, 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.
2. Goto Y. Exercise capacity: Just a powerful prognostic predictor, or a potential therapeutic target in patients with chronic heart failure? Circ J 2015; 79: 2547 – 2548.
3. Carubelli V, Metra M, Corra U, Magri D, Passino C, Lombardi C, et al. Exercise performance is a prognostic indicator in elderly
patients with chronic heart failure: Application of metabolic exercise cardiocadiac indexes score. Circ J 2015;79:2608 – 2615.

4. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1985) 1986; 60: 2020 – 2027.

5. Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 1983; 55: 256 – 264.

6. Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. Int J Cardiol 2019; 288: 107 – 113.

7. Van Iterson EH. Isocapnic buffering: An inconvenient truth in the physiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. J Appl Physiol (1985) 1985; 58: 1901 – 1908.

8. Khoo MC, Kronauer RE, Stropl KP, Slutsky AS. Factors inducing periodic breathing in humans: A general model. J Appl Physiol Respir Environ Exerc Physiol 1982; 53: 644 – 659.

9. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Hasegawa A, et al. The time from anaerobic threshold (AT) to respiratory compensation point reflects the rate of aerobic and anaerobic metabolism after the AT in chronic heart failure patients. Jpn Circ J 1999; 63: 274 – 277.

10. Lahiri S, Hsiao C, Zhang R, Mokashi A, Nishino T. Peripheral chemoreceptors in respiratory oscillations. J Appl Physiol (1985) 1985; 58: 1901 – 1908.

11. Eljadi H, Oshima S, Taniguchi K, Itoh H, Hasegawa A, et al. The time from anaerobic threshold (AT) to respiratory compensation point reflects the rate of aerobic and anaerobic metabolism after the AT in chronic heart failure patients. Jpn Circ J 1999; 63: 274 – 277.

12. Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, et al. Impairment of ventilatory efficiency in heart failure: An ominous sign in patients with chronic heart failure. J Prev Cardiol 2019; 26: 1104 – 1106.

13. Tanehata M, Adachi H, Oshima S, Taniguchi K, Itoh H, Hasegawa A, et al. The time from anaerobic threshold (AT) to respiratory compensation point reflects the rate of aerobic and anaerobic metabolism after the AT in chronic heart failure patients. Jpn Circ J 1999; 63: 274 – 277.

14. Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, et al. Impairment of ventilatory efficiency in heart failure: An ominous sign in patients with chronic heart failure. J Prev Cardiol 2019; 26: 1104 – 1106.

15. Carriere C, Corra U, Piepoli M, Bonomi A, Salvioni E, Binno S, et al. Isocapnic buffering: An inconvenient truth in the physiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. J Appl Physiol (1985) 1985; 58: 1901 – 1908.

16. Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. Int J Cardiol 2019; 288: 107 – 113.

17. Van Iterson EH. Isocapnic buffering: An inconvenient truth in the physiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. J Appl Physiol (1985) 1985; 58: 1901 – 1908.

18. Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, et al. Impairment of ventilatory efficiency in heart failure: An ominous sign in patients with chronic heart failure. J Prev Cardiol 2019; 26: 1104 – 1106.

19. Carriere C, Corra U, Piepoli M, Bonomi A, Salvioni E, Binno S, et al. Isocapnic buffering: An inconvenient truth in the physiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. J Appl Physiol (1985) 1985; 58: 1901 – 1908.

20. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1985) 1986; 60: 2020 – 2027.

21. Itoh H, Koike A, Taniguchi K, Marumo F. Severity and pathophysiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. Jpn Circ J 1989; 53: 146 – 154.

22. Wasserman K. Principles of exercise testing and interpretation: Including pathophysiology and clinical applications. 5th edn. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.

23. Chua TP, Ponikowski P, Webb-Peploe K, Harrington D, Anker SD, Piepoli M, et al. Clinical characteristics of chronic heart failure patients with an augmented peripheral chemoreflex. Eur Heart J 1997; 18: 480 – 486.

24. Kleber FX, Verheugen GB, Wernecke KD, Bauer U, Opitz C, Wensel R, et al. Impairment of ventilatory efficiency in heart failure: Prognostic impact. Circulation 2000; 101: 2803 – 2809.

25. Cherniack NS, Longobardo GS. Cheyne-Stokes breathing: An instability in physiologic control. N Engl J Med 1973; 288: 956 – 957.

26. Ponikowski P, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: Clinical implications and role of augmented peripheral chemosensitivity. Circulation 1999; 100: 2418 – 2424.

27. Murphy RM, Shah RV, Malhotra A, Pappagianopoulos PP, Hough SS, Systrom DM, et al. Exercise oscillatory ventilation in systolic heart failure: An indicator of impaired hemodynamic response to exercise. Circulation 2011; 124: 1442 – 1451.

28. Ponikowski P, Chua TP, Anker SD, Francis DP, Doehner W, Banasiak W, et al. Peripheral chemoreceptor hypersensitivity: An ominous sign in patients with chronic heart failure. Circulation 2001; 104: 544 – 549.

29. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999; 341: 949 – 954.

30. Francis J. Why patients with heart failure die: Hemodynamic and functional determinants of survival. Circulation 1987; 75: 1IV20 – 1IV27.

31. Roul G, Mouilhon ME, Baireis P, Gries P, Sacrez J, Germain P, et al. Exercise peak VO2 determination in chronic heart failure: Is it still of value? Eur Heart J 1994; 15: 495 – 502.

32. Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arhythmias, and plasma noradrenaline as determinants of prognosis in heart failure: The V-HeFT VA Cooperative Studies Group. Circulation 1993; 87: V15 – V116.

33. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality: CONSENSUS Trial Study Group. Circulation 1990; 82: 1730 – 1736.

34. Cunningham DJ, Hey EN, Patrick JM, Lloyd BB. The effect of noradrenaline infusion on the relation between pulmonary ventilation and the alveolar PO2 and PCO2 in man. Ann NY Acad Sci 1963; 109: 756 – 771.

35. Floras J. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. Am Coll Cardiol 1993; 22: 72A – 84A.

36. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JA, 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. J Cardiopulm Rehabil Prev 2007; 27: 121 – 129.

37. Arena R, Guazzi M, Cahalin LP, Myers J. Revisiting cardiopulmonary exercise testing applications in heart failure: Aligning evidence with clinical practice. Exerc Sport Sci Rev 2014; 42: 153 – 160.

38. Ushigome R, Sakata Y, Nochioka K, Miyata S, Miura M, Tadaki S, et al. Temporal trends in clinical characteristics, management and prognosis of patients with symptomatic heart failure in Japan: Report from the CHART-2 study. Circ J 2015; 79: 2396 – 2407.

39. Bohm M, Swedberg K, Komajda M, Borer J, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010; 376: 886 – 894.

40. He SW, Wang LX. The impact of anemia on the prognosis of chronic heart failure: A meta-analysis and systematic review. Congest Heart Fail 2009; 15: 123 – 130.

41. Yamuchi T, Sakata Y, Takada T, Nochioka K, Miura M, Tadaki S, et al. Prognostic impact of anemia in patients with chronic heart failure: With special reference to clinical background: Report from the CHART-2 study. Circ J 2015; 79: 1984 – 1993.

42. Memon I, Norris KC, Bombaske A, Peralta C, Li S, Chen SC, et al. The association between parathyroid hormone levels and homocysteine in diabetic and non-diabetic participants in the National Kidney Foundation’s Kidney Early Evaluation Program. Cardiovasc Med 2013; 3: 120 – 127.