Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

Comparative determination of ventilatory efficiency from constant load and incremental exercise testing

S. Algul[1*], F. A. Ugur[2], A. Ayar[3], O. Ozcelik[2]

[1] Faculty of Medicine, Department of Physiology, Yuzuncu Yil University, Van, Turkey
[2] Faculty of Medicine, Department of Physiology, Firat University, Elazig, Turkey
[3] Faculty of Medicine, Department of Physiology, Karadeniz Technical University, Trabzon, Turkey

Correspondence to: serminalgul@hotmail.com, serminalgul@yyu.edu.tr

Received March 10, 2017; **Accepted** May 18, 2017; **Published** August 15, 2017

Doi: http://dx.doi.org/10.14715/cmb/2017.63.7.4

Abstract: The analysis of the relationships between minute ventilation (V_E) to CO_2 output (VCO_2), referred to as ventilatory efficiency, in response to incremental exercise testing, is considered a useful index for assessing the presence and severity of cardiopulmonary and metabolic diseases. The effects of constant load exercise testing performed at work intensity associated with anaerobic threshold (AT) and respiratory compensation points (RCP), on the accurate measurements of ventilatory efficiency are not well known. The aim of this present study was to investigate the reliability of the V_E/VCO_2 ratio obtained from constant load exercise tests performed with two important metabolic rates (at the AT and RCP) and compare it to that of those of incremental exercise tests. A total of 20 young male (20.8±0.4 yr) subjects initially performed an incremental exercise test and then two constant load exercise tests, on different days. Respiratory and pulmonary gas exchange variables were used to estimate AT and RCP. A paired *t*-test was used to analyse data. AT and RCP (average) occurred the at 60% and at 71% of peak O_2 uptake, respectively. The lowest V_E/VCO_2 ratio recorded within the first 2 minutes of constant load exercise tests with a work load of AT (26.4±0.3) and RCP (26.7±0.5) was not statistically different from the lowest ratio obtained from the incremental exercise tests (26.0±0.7). In the constant load exercise test, despite the different metabolic rates, the increase in ventilation corresponded closely with the increase in CO_2 production, reflecting an optimal ventilation and perfusion ratio. Clinicians should consider the constant load exercise test work load associated with AT and RCP as it provides a meaningful lowest value for ventilatory efficiency.

Key words: Exercise; Anaerobic threshold; Respiratory compensation point; Ventilatory efficiency; Ventilation.

Introduction

Cardiopulmonary exercise testing is an effective tool for evaluating the substantiality of cardiovascular, respiratory, and metabolic systems functions in healthy individuals and patients, including those with acute or chronic illnesses (1, 2). Incremental exercise testing is frequently performed to objectively measure three important parameters: the transition point from aerobic to anaerobic metabolism (i.e. anaerobic threshold, AT), the onset of metabolic acidemia induced hyperventilation (i.e. respiratory compensation point, RCP) and the peak O_2 uptake (VO_{2peak}) capacity (2).

The VO_{2peak} (3) and/or VO_2 at the AT (4, 5) have been considered valuable indices in determining patients' prognosis. The RCP is the critical metabolic turning point that reflects the highest tolerated metabolic rate for long durations (6, 7).

In addition, measurement of the slope (or ratio) of ventilation (V_E) relative to CO_2 output (VCO_2) during incremental exercise below the respiratory compensation point (RCP) (V_E/VCO_2), called ventilatory efficiency (8), can be used as an important prognostic criteria in patients with heart (9, 10) or lung diseases (11). Ventilatory efficiency reflects the sensitivity of matching of ventilation and perfusion (8) and is possible to be measured across different age groups from pediatrics to adolescents (12).

During an incremental exercise test, there is a gradual increase in metabolic rate and ventilatory response. Ventilation increases in close relationship with the increase in VCO_2 until the RCP is reached. However, above the RCP, V_E increases rapidly compared to VCO_2 and the V_E/VCO_2 slope (ratio) becomes steeper (2, 13). During an incremental exercise test, the lowest V_E/VCO_2 ratio that is generally possible to be achieved in the RCP that reflects the status of ventilatory efficiency. The severity of ventilation perfusion mismatch in patients with impaired heart or lung functions causes a higher V_E/VCO_2 slope (or ratio) (9, 14). It has been suggested that the prognostic power of the V_E/VCO_2 ratio is more powerful than that of peak VO_2 data in cardiac patients (14, 15).

Constant load exercise testing with two different exercise intensities (AT and RCP) and corresponding metabolic demands may also provide valuable information concerning the response of the V_E/VCO_2 ratio, when compared to the incremental exercise test. So far, to our knowledge, there is no study that evaluates the V_E/VCO_2 relationship during constant load exercise testing that corresponded to AT and/or RCP, that then compares the results with those obtained in an incremental exercise test.

The aim of this study was to evaluate the ventilatory

Table 1. The mean (±SE) values for work rate (W), heart rate (HR), O_2 uptake for each kilogram of body weight (VO_2BW), minute ventilation (V_E), O_2 uptake (VO_2), CO_2 output (VCO_2), minute ventilation to O_2 uptake (V_E/VO_2) ratio, minute ventilation to CO2 output ratio (V_E/VCO_2) at warm up (W_{20}), at the anaerobic threshold (W_{AT}), at the respiratory compensation point (W_{RCP}), and at the maximal exercise performance (W_{max}) during an incremental exercise test.

	W_{20}	W_{AT}	W_{RCP}	W_{max}
WR (W)	20	129±4	155±5	220±5
HR (beat/min)	92±2	133±3	150±3	189±1.0
VO_2BW (mL/min/kg)	9.11±0.2	24.46±0.8	28.62±0.9	40.01±1.0
V_E (L/min)	18.9±0.5	46.7±2.7	58.6±3.4	106.4±4.8
VO_2 (L/min)	0.685±0.02	1.831±0.05	2.143±0.06	3.005±0.07
VCO_2 (L/min)	0.627±0.02	1.792±0.06	2.250±0.08	3.575±0.10
V_E/VO_2	28.7±0.9	25.5±0.8	27.3±1.0	35.4±1.2
V_E/VCO_2	30.1±0.9	26.0±0.8	26.0±0.7	29.7±1.1

efficiency (i.e. the lowest values of V_E/VCO_2) response to constant load exercise tests performed at the AT and RCP, and that then compares the results with the those of obtained from an incremental exercise test.

Materials and Methods

Twenty healthy young male subjects (age: 20.8±0.4 yr, height: 184±2 cm, weight: 75.3±1.2 kg and body mass index: 22.2±0.4 kg/m^2) agreed to participate in the investigation and signed written informed consent forms, which were approved by the institutional ethics committee.

Testing conditions between experiments were standardised for each subject: tests were conducted at the same time of day (between 08:00 to 10:00); after a period of overnight fasting (or a light meal was taken at a similar time prior to arrival at the laboratory, no sooner than 2 hour before testing). Before the test, the subjects' height and body weight were measured (Tanita, TBF 300 M, Japan). The exercise tests were performed in a climatically controlled laboratory where the temperature was kept at around 22ºC. The subjects were introduced to the laboratory environment and the protocol of experiment they would undergo. The subjects were requested to refrain from smoking, or consuming alcohol or caffeine. They were asked to avoid strenuous exercise for a period of 12 hours prior to testing.

Each subject performed an incremental exercise test to exhaustion (16) on an electromagnetically braked cycle ergometer (VIA sprint TM150/200P). The exercise test consisted of an initial period of 4 minutes of cycling at the 20 W as a warm-up, followed by an increase of power at 15 W/min to the limit of the subject's tolerance. The pedalling frequency was between 50 and 70 rpm (average 60 rpm). Seat and handlebar heights were set for each subject. Prior to the work load application, the subjects were controlled carefully for non-specific hyperventilation to avoid the pseudo-threshold phenomenon (17). Then each subject performed two random constant load exercise tests on different days (with at least three day between each test): these consisted of an initial period of 4 minutes of cycling at the 20 W as a warm-up, followed by an increasing rate of power at the AT and/or RCP. The exercise time for the constant load exercise was consisted a period of 15 minutes to avoid substrate alteration to ventilation and subjects' ventilatory efficiency becoming stable.

The VO_{2peak} was measured at the highest O_2 level attained at the end of the ramp test. The AT was estimated non-invasively, using a cluster of standard gas exchange indices (18): the break-point in the VCO_2/VO_2 relationship (the 'V-slope' technique) (19); the increase in ventilatory equivalent for O_2 uptake (V_E/VO_2) and end-tidal partial pressure of O_2 ($P_{ET}O_2$) without a corresponding increase in ventilatory equivalent for CO_2 (V_E/VCO_2) and decrease in end-tidal partial pressure of CO_2 ($P_{ETC}O_2$) (2, 18). The RCP was determined by observing the point where the increase in ventilatory equivalent for CO_2 ($P_{ET}CO_2$) and decrease in end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) occurred (2, 18).

During the test, the subjects breathed through a low dead-space, low-resistance turbine volume transducer (Triple V-Volume Sensor) for continuous measurement of inspired and expired volumes and flows. The ventilatory and gas exchange parameters of minute ventilation (V_E, BTPS); O_2 uptake (VO_2 , STPD), CO_2 output (VCO_2, STPD), end-tidal O_2 pressure ($P_{ET}O_2$), and end-tidal CO_2 pressure ($P_{ET}CO_2$) were evaluated breath-by-breath using a gas analyser system (Master Screen CPX, Germany). The system was calibrated before each test for temperature, barometric pressure, and O_2 and CO_2 concentrations according to the manufacturer's specifications. Cardiac parameters (including heart rate, ST, T and QT) were followed continuously using a 12 lead ECG. Heart rate was recorded as beat-by-beat throughout the study.

The data are expressed as means (± standard error [SE]). A paired *t*-test was used to analyse the significance of data. A value of $p<0.05$ was accepted as statistically significant.

Results

Table 1 shows the work rate, heart rate, and ventilatory and pulmonary gas exchange variables of subjects during the warm up period, at the AT, at the RCP and at the end of the ramp test. During incremental exercise testing, aerobic to anaerobic metabolic transition (i.e., AT) occurred at 60% of VO_{2peak} and exercise hyperventilation (i.e. RCP) began at 71% of VO_{2peak}. The work production capacity for each kilogram of body weight was found to be 1.71±0.06 W/min/kg for AT, 2.07±0.07 W/min/kg for RCP and 2.92±0.07 W/min/kg for maximal exercise. VO_2 for each kg of body weight was found to be 24.46±0.8 ml/min/kg at the AT 28.62±0.9 ml/min/

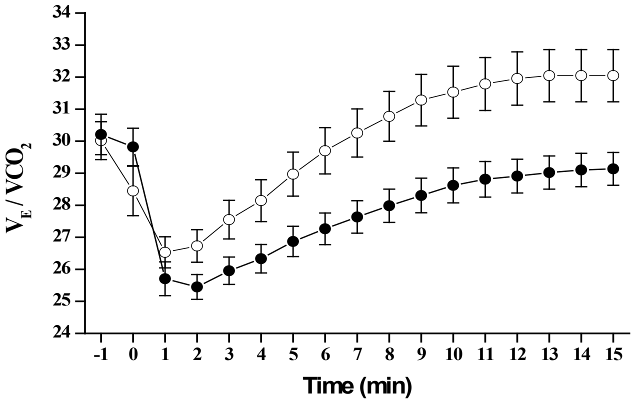

Figure 1. The mean (±SE) values for the minute ventilation to CO_2 output ratio (V_E/VCO_2) during 15 minutes of constant load exercise tests performed at the at the anaerobic threshold (black circle) and at the respiratory compensation point (white circle). The region between -1 to 0 represents the average values for the warm-up period.

kg at the RCP and 40.01±1.0 ml/min/kg at the maximal exercise.

During incremental exercise testing, with an increasing work load, V_E/VCO_2 and V_E/VO_2 decreased to their lowest values at the AT. Beyond the AT, V_E/VCO_2 stabilised above the AT until the RCP, whereas V_E/VO_2 continued to increase (Table 1). The (mean ± SE) V_E/VCO_2 (Figure 1) and V_E/VO_2 (Figure 2) relationships are plotted for AT and RCP for the constant work-rate exercise tests. The lowest V_E/VCO_2 ratio was recorded within 2 minutes of the constant load exercise tests with work load AT (26.4±0.3) and RCP (26.7±0.5). Then they increased and reached the values of 29.1±0.5 (AT) 32.0±0.8 (RCP).

There was no significant differences in the lowest values of V_E/VCO_2 observed during the constant load exercise test and in RCP during the incremental test (Figure 3). However, the V_E/VCO_2 ratio at the end of the constant load exercise test was significantly higher than that obtained from the ramp test (Figure 3).

The V_E/VO_2 ratio showed different responses to the applied work load intensity. In the constant load exercise performed at the AT, the V_E/VO_2 ratio varied between 21.8 to 29.7. There was no significantly differences between the lowest value obtained from the constant load exercise test (25.5±0.5) and the lowest value observed in the incremental test (25.5±0.8). However, there were significant differences between the lowest V_E/VO_2 values obtained at the RCP from constant load exercise (between 17.6 and 27) and from the incremental ramp test ($p<0.0001$). The significantly difference in lowest V_E/VO_2 values was observed between the AT (25.5±0.5) and RCP (22.5±0.7) ($p < 0.05$) in the constant load exercise test. At the end of the constant load testing, V_E/VO_2 was found to be 29.4±0.6 for the AT and 30.9±0.9 for the RCP.

Discussion

The intention of our study was to evaluate the prognostic sensitivity of the lowest V_E/VCO_2 ratio in constant load exercise testing associated with work load AT (2) and RCP (20) both of which are important set point for exercise. In the present study we used the V_E/VCO_2

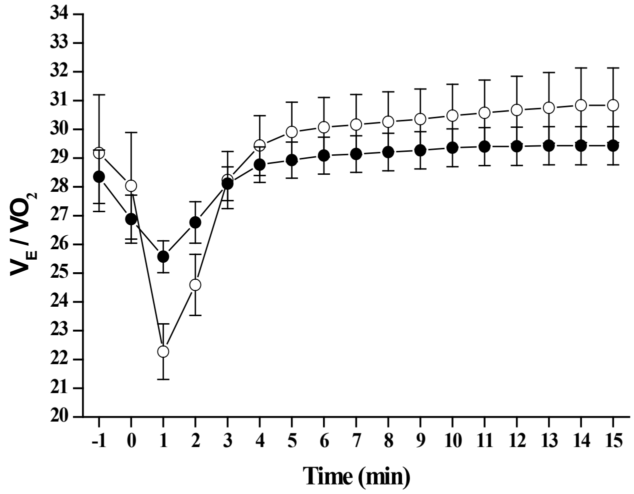

Figure 2. The mean (±SE) values for the minute ventilation to O_2 uptake ratio (V_E/VO_2) during 15 minutes of constant load exercise tests performed at the at the anaerobic threshold (black circle) and at the respiratory compensation point (white circle). The region between -1 to 0 represents the average values for the warm-up period.

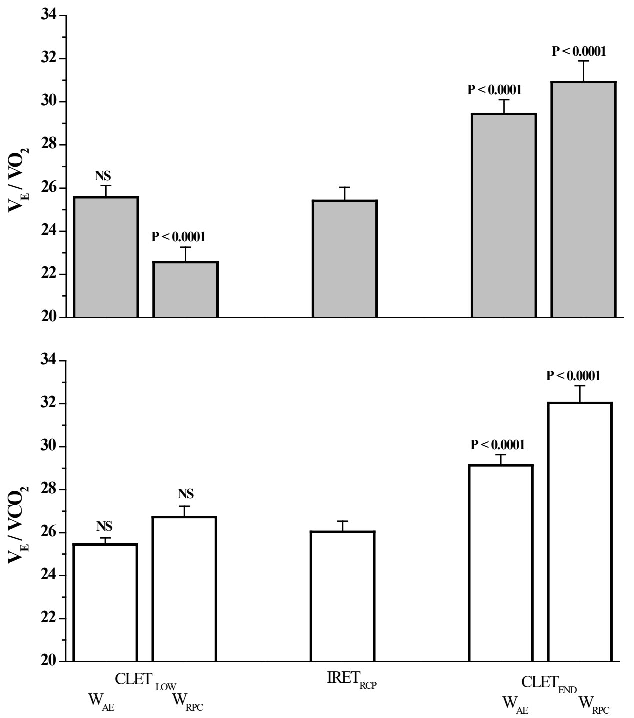

Figure 3. The mean (±SE) values for the minute ventilation to O_2 uptake ratio (V_E/VO_2, grey column), and minute ventilation to CO_2 output ratio (V_E/VCO_2, white column) at the respiratory compensation point of the incremental exercise test ($IRET_{RCP}$), lowest values ($CLET_{LOW}$), and end of exercise values ($CLET_{END}$), for constant load exercise tests performed at the anaerobic threshold (W_{AE}), and at the respiratory compensation point (W_{RCP}).

ratio instead of slope that is shown not significantly different (8). The lowest values for V_E/VCO_2 ratio at two different metabolic rates (i.e. AT and RCP) were similar to the obtained from the incremental ramp exercise test (Figure 3)

The V_E/VCO_2 ratio in normal subjects is an indicator of ventilatory sensitivity that is influenced by peripheral and central chemoreceptors (21) and changes in dead space (22). Typically, in clinical medicine, a rapid incremental exercise test is the first choice for evaluating the V_E and VCO_2 (V_E/VCO_2) relationship (23). During an incremental exercise test with breathing hypoxic gas, increased ventilatory equivalents have been shown (24). The V_E/VCO_2 relationship ratio has not been widely studied in constant load exercise tests associated with AT and RCP in normal subjects.

The work production capacity and VO_2 levels for each kilogram of body weight at the AT, at the RCP and at maximal exercise capacity showed the fitness status of the subjects (25). In normal healthy subjects, the V_E/VCO_2 ratio (or slope) is usually recorded within a range of approximately 24 to 34 (2). In the study, we have found that the V_E/VCO_2 ratio varied between 20 to 30 in both exercise set points (AT and RCP). An important consideration is that a V_E/VCO_2 slope above 34 can be used as a prognostic indicator of ventilatory inefficiency.

An increased ratio of dead space to tidal volume (11) and a ventilation perfusion mismatch (9) in patients with impaired heart or lung functions are the main reasons for an increased V_E/VCO_2 slope. It is important to emphasise that, many patients with cardiac or pulmonary function disease may not be able to perform an incremental exercise test to maximal effort, and therefore may be unable to achieve an acceptable prognostic V_E/VCO_2 slope. In the literature, it has been suggested that an exercise test below the 50% of RCP may provide an adequate, prognostic V_E/VCO_2 slope (26). The results of this study suggest that the application of moderate intensity (i.e. intensity corresponded to the AT) constant load exercise testing will provide an acceptable data for the V_E/VCO_2 ratio (Figure 2). A significant correlation has been shown between V_E/VCO_2 slope and ratio (2, 8). A high levels of mortality rate has been reported in patients undergoing major abdominal surgery with a V_E/VCO_2 value above 34 and VO_2 at the AT below 11 ml/min/kg (4). In addition, a high risk of death in the postoperative period has been reported in patients with a V_E/VCO_2 ratio above 42 (27).

At the end of constant load exercise, the V_E/VCO_2 ratio is higher in RCP compared to AT. The stable V_E/VCO_2 ratio during constant load exercise shows a higher tolerable and sustainable point for ventilation and perfusion matching. This could be another set point for evaluating subjects' fitness status, in addition to the lowest value of V_E/VCO_2.

The evaluation of ventilatory efficiency from the V_E/VO_2 ratio during constant load exercise testing may not indicate an acceptable outcome (Figure 3) (8). The variability of the V_E/VO_2 ratio regarding work load intensity showed a significant difference when compared to the ramp test. The regulation of the ventilatory control mechanism is closely associated with arterial blood pH and CO_2 levels (21). The decrease in the V_E/VCO_2 ratio during the early stage of constant load exercise tests could be the result of a decrease in the dead space to tidal volume ratio that occurs at the AT during incremental exercise testing (28).

The non-invasive measurements of ventilatory efficiency from the V_E/VCO_2 relationship during a constant load exercise test of moderate intensity can provide useful information for identifying the severity of heart or lung diseases. To indicate the clinical efficacy of the lowest and most stable V_E/VCO_2 ratio during constant load exercise testing performed at the AT, further research is needed to analyse these findings in subjects with impaired lung, heart, or metabolic system functions.

Author's contribution

We gratefully declare that all authors participated in the study design, data collection, data analysis, manuscript preparation and revision and agree to be accountable for all aspects of the work.

References

1. Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J 2007; 29:185-209.

2. Wasserman K, Hansen JE, Sue DY, Stringer W, Sietsema KE, Sun XG, et al. Principles of Exercise Testing and Interpretation: Including Pathophysiolgy and Clinical Applications, Lippincott Williams & Wilkins, Philadelphia, PA, USA, 5th edition, 2012.

3. Kato TS, Collado E, Khawaja T, Kawano Y, Kim M, Farr M, et al. Value of peak exercise oxygen consumption combined with B-type natriuretic peptide levels for optimal timing of cardiac transplantation. Circ Heart Fail 2013; 6:42.

4. West M, Jack S, Grocott MP. Perioperative cardiopulmonary exercise testing in the elderly. Best Pract Res Clin Anaesthesiol 2011; 25: 427-37.

5. Agostoni P, Corrà U, Cattadori G, Veglia F, Battaia E, La Gioia R, et al. MECKI Score Research Group. Prognostic value of indeterminable anaerobic threshold in heart failure. Circ Heart Fail 2013; 6:977-87.

6. Keir DA, Fontana FY, Robertson TC, Murias JM, Paterson DH, Kowalchuk JM, et al. Exercise intensity thresholds: identifying the boundaries of sustainable performance. Med Sci Sports Exerc 2015; 47:1932-40.

7. Maciejczyk M, Szymura J, Cempla J, Gradek J, Więcek M, Bawelski M. Respiratory compensation point during incremental test in overweight and normoweight boys: is it useful in assessing aerobic performance? A longitudinal study. Clin Physiol Funct Imaging 2014; 34:56-63.

8. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 2002; 166:1443-8.

9. Hoshimoto-Iwamoto M, Koike A, Nagayama O, Tajima A, Uejima T, Adachi H, et al. Determination of the V_E/VCO_2 slope from a constant work rate exercise test in cardiac patients. J Physiol Sci 2008; 58:291-5.

10. Mazaheri R, Shakerian F, Vasheghani-Farahani A, Halabchi F, Mirshahi M, Mansournia MA. The usefulness of cardiopulmonary exercise testing in assessment of patients with suspected coronary artery disease. Postgrad Med J 2016; 92:328-32.

11. Neder JA, Arbex FF, Alencar MC, O'Donnell CD, Cory J, Webb KA, et al. Exercise ventilatory inefficiency in mild to end-stage COPD. Eur Respir J 2015; 45:377-87.

12. Parazzi PL, Marson FA, Ribeiro MA, Schivinski CI, Ribeiro JD. Ventilatory efficiency in children and adolescents: A systematic review. Dis Markers 2015; 2015:546891.

13. Whipp BJ, Davis JA, Wasserman K. Ventilatory control of the 'isocapnic buffering' region in rapidly-incremental exercise. Respir Physiol 1989; 76:357-67.

14. Koike A, Itoh H, Kato M, Sawada H, Aizawa T, Fu LT, et al. Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. Chest 2002; 121:1581-8.

15. Poggio R, Arazi HC, Giorgi M, Miriuka SG. Prediction of severe cardiovascular events by V_E/VCO_2 slope versus peak VO_2 in systolic

heart failure: a meta-analysis of the published literature. Am Heart J 2010; 160:1004-14.
16. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. J Appl Physiol Respir Environ Exerc Physiol 1981; 50:217-21.
17. Ozcelik O, Ward SA, Whipp BJ. Effect of altered body CO_2 stores on pulmonary gas exchange dynamics during incremental exercise in humans. Exp Physiol 1999; 84:999-1011.
18. Whipp BJ, Ward SA, Wasserman K. Respiratory markers of the anaerobic threshold. Adv Cardiol 1986; 35:47-64.
19. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986; 60:2020-7.
20. Algul S, Ozcelik O, Yilmaz B. Evaluation of relationship between aerobic fitness level and range of isocapnic buffering periods during incremental exercise test. Cell Mol Biol (Noisy le Grand) 2017; 63: 78-82.
21. Whipp BJ, Ward SA. Determinants and control of breathing during muscular exercise. Br J Sports Med 1998; 32:199-211.
22. Ward SA, Whipp BJ. Ventilatory control during exercise with increased external dead space. J Appl Physiol Respir Environ Exerc Physiol 1980; 48:225-31.
23. Davis JA, Sorrentino KM, Soriano AC, Pham PH, Dorado S. Is ventilatory efficiency dependent on the speed of the exercise test protocol in healthy men and women? Clin Physiol Funct Imaging 2006; 26:67-71.
24. Ozcelik O, Kelestimur H. Effects of acute hypoxia on the estimation of lactate threshold from ventilatory gas exchange indices during an incremental exercise test. Physiol Res 2004; 53;653-9.
25. Ozcelik O, Aslan M, Ayar A, Kelestimur H. Effects of body mass index on maximal work production capacity and aerobic fitness during incremental exercise. Physiol Res 2004; 53:165-70.
26. Ingle L, Goode K, Carroll S, Sloan R, Boyes C, Cleland JG, et al. Prognostic value of the V_E/VCO_2 slope calculated from different time intervals in patients with suspected heart failure. Int J Cardiol 2007; 118:350-5.
27. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. Br J Surg 2007; 94:966-9.
28. Whipp BJ. Physiological mechanisms dissociating pulmonary CO_2 and O_2 exchange dynamics during exercise in humans. Exp Physiol 2007; 92:347-55.