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EFFECT OF EXERCISE TESTING PROTOCOL ON THE RELATIONSHIP BETWEEN MINUTE VENTILATION AND CARBON DIOXIDE PRODUCTION

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ABSTRACT

Background: The effect of exercise protocol on the slope of the relationship between minute ventilation and carbon dioxide production ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) has not fully been studied. *Methods:* Twenty-five healthy volunteers performed two sessions of incremental bicycle exercise, one with a rapidly increasing staged (RIS: 25W every minute) protocol and another with a slowly increasing staged (SIS: 25W every 3 minutes) protocol to calculate the $\Delta\dot{V}E/\Delta\dot{V}CO_2$. Six of the subjects also participated in sessions of steady state exercise (SSE) test various work rates. *Results:* The $\Delta\dot{V}E/\Delta\dot{V}CO_2$ was significantly lower when the RIS protocol was used than when the SIS protocol was used (23.3±2.3 vs. 24.9±1.8, $p<0.001$). Data from the subjects who also underwent SSE sessions revealed that the $\Delta\dot{V}E/\Delta\dot{V}CO_2$ from the SSE protocols was greater than that from the RIS protocol and identical with that from the SIS protocol (25.1±3.7, 20.6±1.7, and 24.0±2.7, respectively, $p<0.05$), while arterial partial pressure of carbon dioxide during exercise was not different between the protocols (43.0±3.3, 39.9±2.1, and 40.8±2.6, respectively, n.s.). *Conclusions:* Care must be taken in the interpretation of the values of $\Delta\dot{V}E/\Delta\dot{V}CO_2$, as they are influenced by the difference in exercise protocol.

Key Words: exercise, exercise testing, ventilatory response, reliability

INTRODUCTION

Abnormal ventilatory response to exercise (shortness of breath or excess ventilation during exercise) is one of the most common symptoms in patients with chronic congestive heart failure.[1-6] The slope of the relationship between minute ventilation and carbon dioxide production during incremental exercise testing ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) is the most widely used and considered to be the most reliable method to evaluate the degree of abnormal ventilatory response to exercise.[5,7-11] This measurement is theoretically based on the alveolar ventilation equation.[9,12] However, as the equation holds good only during the steady state condition of exercise,[12,13] the validity of the measurement derived from incremental exercise testing, especially when we use rapidly increasing staged exercise protocols, is questioned. At present, regrettably, various exercise protocols are used without critical examination to obtain this measurement, and the validity of using

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incremental protocols and the agreement of the measurements between various exercise protocols remains unstudied. The aim of the this paper is, therefore, to study how well the measurements of $\Delta\dot{V}E/\Delta\dot{V}CO_2$ obtained from various incremental exercise protocols agree with those from steady state exercise protocols.

MATERIALS AND METHODS

Subjects

A total of 25 healthy normal Japanese volunteers (14 male and 11 female), who were recruited from our university, participated in the study. Their mean age was 22±5 years old (range: 18 to 43 years old), and mean body mass was 59±8 kg (range: 48 to 73 kg). Physician interviews and physical examinations revealed that they were in good health. All subjects were sedentary or moderately active (six tennis players, two karate practitioners, five swimmers, and three joggers), but did not participate in daily exercise events at competitive levels. Written informed consent was obtained from each participant. The ethics committee of our institute approved this study.

Exercise testing

Exercise testing was conducted usually between 14:00 and 18:00 o'clock at least 3 hours after a light meal. Three of the subjects were habitual smokers; they were instructed to refrain from smoking at least 3 hours before testing. An electromagnetically braked cycle ergometer (P. K. Morgan, UK) was used for the test with the subjects pedaling at a constant rate of 60 rev/min. Three different exercise protocols were used in the present study: a rapidly increasing staged protocol, a slowly increasing staged protocol, and series of steady state sessions with different work rates (Figure 1). The exercise tests were conducted at the same hour of the day with an interval between testing sessions of no more than 3 days. The order of the tests was randomly assigned. In the rapidly increasing staged exercise testing (25 watts every minutes), exercise was initiated with 1 minute of unloaded cycling followed by a uniform increase in work rate of 25 watts/min until exhaustion. In the slowly increasing staged exercise protocol (25 watts every 3 minutes), the work rate increment was the same (25 watts), but the duration of each stage was 3 minutes.

The last six subjects of the study agreed to participate in a series of steady state bicycle exercise sessions with various work rates, in addition to the two incremental test sessions, to clarify whether one of the two incremental protocols produces more accurate results that are closer to the "gold standard". The duration of each session was 10 minutes. The work rate for the first steady state exercise testing session was 25 watts. The second steady state exercise session was conducted with a work rate of 50 watts after an interval of at least one hour. The subsequent steady state exercise sessions were conducted in the same manner with an increment in work rate of 25 watts until arterial lactate concentration exceeded 4 mmol/l.

Analysis of Expired Gas

Subjects breathed through a Hans Rudolph low-resistance nonrebreathing valve. Carbon dioxide production ($\dot{V}CO_2$, [ml/min, STPD]), oxygen uptake ($\dot{V}O_2$, [ml/min, STPD]), minute ventilation ($\dot{V}E$, [l/min, BTPS]), tidal volume (l, BTPS), respiratory rate (breaths per minute), and the mixed expiratory carbon dioxide concentration (%) were continuously measured on a breath-by-breath basis with the Benchmark Metabolic Measurement Cart (P. K. Morgan, UK) equipped with an oxygen and carbon dioxide analyzer.

The $\Delta\dot{V}E/\Delta\dot{V}CO_2$ was calculated with the use of linear regression analysis between $\dot{V}E$ and $\dot{V}CO_2$.[7,8] For the calculation of the $\Delta\dot{V}E/\Delta\dot{V}CO_2$ derived from the two incremental protocols, gas

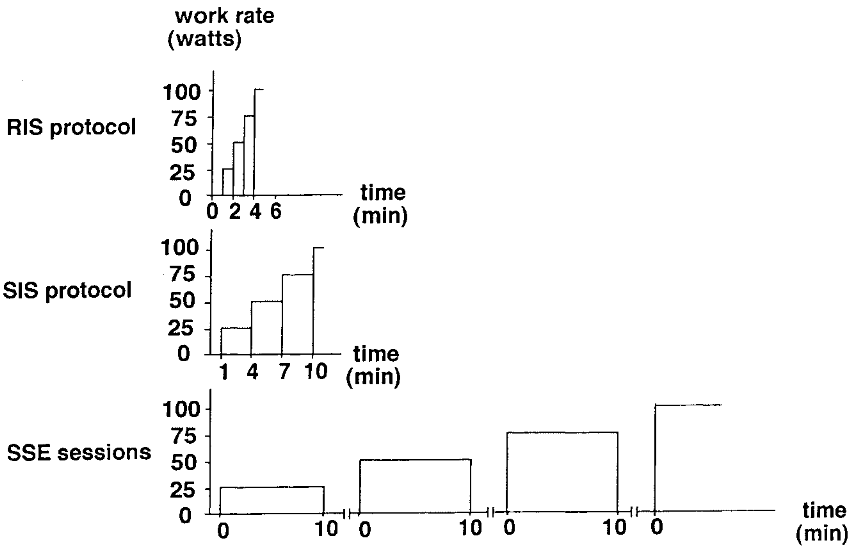

Figure 1: Schematic description of the exercise protocols used in the present study. In the rapidly increasing staged exercise testing (RIS protocol), exercise was initiated with 1 minute of unloaded cycling followed by a uniform increase in work rate of 25 watts/min until exhaustion (upper panel). In the slowly increasing staged exercise protocol (SIS protocol), the work rate increment was the same (25 watts), but the duration of each stage was 3 minutes (middle panel). The duration of each steady state exercise (SSE) session was 10 minutes. The work rate for the first steady state exercise testing was 25 watts. The second steady state exercise session was conducted with a work rate of 50 watts after an interval of at least one hour. The subsequent steady state exercise sessions were conducted in the same manner with an increment in the work rate of 25 watts until arterial lactate concentration exceeded 4 mmol/l (lower panel).

analysis data from the beginning of the incremental part of exercise testing to the beginning of respiratory compensation, the point after which continuous increase in the $\dot{V}E/\dot{V}CO_2$ ratio occurred, were used. As for steady state exercise testing, the final 1-minute average data of each session were used for the calculation.

Arterial blood gas and lactate analysis

The last six subjects of the study had a flexible catheter placed in the brachial artery prior to the testing. Arterial blood samples were drawn from the catheter after the work rate in the incremental testing had reached 75 watts. Blood samples were also collected 1 minute before the end of the 75-watt steady state exercise testing. Arterial blood gas was measured with a Ciba-Corning 278 Blood Gas System. Arterial lactate concentration was measured immediately after the sampling with a lactate analyzer (YSI 2300 Stat Plus, Yellow Springs, U.S.A.).

Degree of perceived exertion

All subjects reported their Borg scale level of perceived exertion when the incremental exercise had reached the somewhat hard or rather hard stages, 200 watts for male and 150 watts for female subjects.

Statistical analysis

Values were expressed as the mean ± SD. Comparisons of mean values of $\Delta\dot{V}E/\Delta\dot{V}CO_2$ between the two incremental protocols were tested by paired *t*-test. Differences in the measurements between the three protocols were tested with one-way analysis of variance for repeated

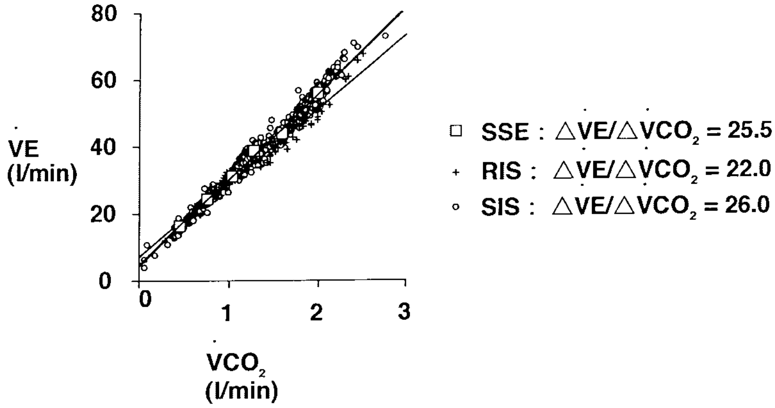

Figure 2: A graph showing the relationships between minute ventilation ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$) obtained from a representative subject (a 22-year-old male). The regression slope ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) obtained from the slowly increasing staged (SIS) protocol was almost identical with that from steady state exercise (SSE) sessions, whereas the slope from the rapidly increasing staged protocol was smaller.

measurements. If significant differences were detected by the F test, multiple comparisons were analyzed by the Dunnett *t*-test. Borg scale comparisons were made by Wilcoxon's rank sum test. A p value < 0.05 was considered statistically significant.

RESULTS

The $\Delta\dot{V}E/\Delta\dot{V}CO_2$ was significantly lower when the rapidly increasing staged protocol was used than when the slowly increasing staged protocol was used (23.3±2.3 vs. 24.9±1.8, n=25, $p<0.001$). Data from the subjects who also underwent steady state exercise sessions confirmed the result: the rapidly increasing staged protocol resulted in lower values for the $\Delta\dot{V}E/\Delta\dot{V}CO_2$ than either the slowly increasing staged protocol or the steady state exercise protocols did (20.6±1.7, 24.0±2.7, and 25.1±3.7, respectively, n=6, $p<0.05$) (Figure 2). Borg scale scores at the exercise intensity of 200 watts for men or 150 watts for women were greater in the slowly increasing staged protocol than the rapidly increasing staged protocol ($p<0.001$). On the other hand, arterial partial pressure of carbon dioxide during exercise was not different between the protocols (43.0±3.3 mmHg, 39.9±2.1 mmHg, and 40.8±2.6 mmHg, respectively, n=6, n.s.).

DISCUSSION

This study demonstrates that the $\Delta\dot{V}E/\Delta\dot{V}CO_2$ is influenced by the difference in exercise protocol: the rapidly increasing staged protocol led to lower values of the slope than either the slowly increasing staged protocol or the steady state exercise protocols.

It is well known that there is a strong correlation between $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise.[7,8,10,11,14] The slope of the regression line ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) is considered to be an index of ventilatory response to exercise,[7,8,10,11,14] with a steeper slope indicating excessive exercise ventilation, a symptom characteristic of congestive heart failure.[1-5,15,16]

The $\Delta\dot{V}E/\Delta\dot{V}CO_2$ is theoretically based on the alveolar ventilation equation modified by Whipp[17]:

$\dot{V}E = 863\ \dot{V}CO_2\ /\ PaCO_2\ (1 - Vd/Vt)$,

where $PaCO_2$ is arterial carbon dioxide partial pressure, Vd/Vt is the ratio of dead space ventilation to tidal volume, and 863 is a constant to standardize gas measurements to body temperature, pressure, and saturation. The differential of this equation by VCO_2 yields

$dVE/dVCO_2 = 863\ /\ PaCO_2\ (1 - Vd/Vt)$,

where $dVE/dVCO_2$ represents the $\Delta\dot{V}E/\Delta\dot{V}CO_2$ itself. This equation shows that factors that determine the $\Delta\dot{V}E/\Delta\dot{V}CO_2$ are dead space fraction and $PaCO_2$ during exercise. Excessive exercise ventilation, or increased $\Delta\dot{V}E/\Delta\dot{V}CO_2$, in patients with chronic congestive heart failure is mainly explained by increased dead space ventilation,[7,11] while the contribution of reduced $PaCO_2$ during exercise remains in dispute.[13]

A major theoretical problem, however, in using the alveolar ventilation equation is that the equation is valid only when steady state conditions of metabolic gas exchange are attained.[16] Therefore, the use of incremental exercise protocols to obtain $\Delta\dot{V}E/\Delta\dot{V}CO_2$ may lead to erroneous results. The present study shows that the use of rapidly increasing staged protocols leads to significantly lower values of $\Delta\dot{V}E/\Delta\dot{V}CO_2$ than steady state protocols, which are considered to be the "gold standard." On the other hand, the slowly increasing staged protocol resulted in values similar to the steady state exercise. This may be accounted for by the difference in $PaCO_2$ during exercise, which was not proved to be different in the present study. These results demonstrate that the difference in $\Delta\dot{V}E/\Delta\dot{V}CO_2$ between protocols is explained by whether a steady state condition is attained during exercise testing, rather than the difference in $PaCO_2$ during exercise.

There are some limitations to the present study. First, since we used healthy subjects, it may not be possible to extrapolate the data to patients with heart failure. Some of the subjects were exercising regularly, although not competitively. Exercise training can affect the relationship between $\dot{V}E$ and $\dot{V}CO_2$, or the effect of exercise protocols on their relationship. Another limitation of the present study is that there may be some bias in the selection of the study subjects who participated in the steady state exercise sessions, as their $\Delta\dot{V}E/\Delta\dot{V}CO_2$ obtained from the RIS protocol (20.6±1.7) was somewhat lower than of the 25 study subjects overall (23.3±2.3). However, the results from the six subjects who also participated in the steady state exercise sessions agreed with those from all 25 subjects in that the RIS protocol resulted in significantly lower $\Delta\dot{V}E/\Delta\dot{V}CO_2$ than the other two protocols. We therefore believe that this potential bias would not crucially affect the principal findings of this study.

In summary, care must be taken in the calculation and interpretation of the values of $\Delta\dot{V}E/\Delta\dot{V}CO_2$, as they are influenced by the difference in exercise protocol. As erroneous measurements may result from rapidly increasing protocols, the duration of each stage must be sufficiently long so that a steady state condition of exercise is reached.

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