

การศึกษาเบื้องต้นของการตอบสนองของการระบายอากาศขณะ ออกกำลังกายสูงสุดในประชากรไทยสุขภาพดี

ทิชานนท์ พรหมศรีสุข¹, วิลัยวรรณ กฤษณะพันธ์¹, อรพิน ผาสุริย์วงศ์¹, วัชรา บุญสวัสดิ์², บุญส่ง พัจจนสุนทร², บุรพา ปุสธธรรม², ฌัญญา ม่วงฤทธิ์เดช¹, จิราพร แข็งขัน¹, พุทธิพล ชาญฉลาด¹

¹ภาควิชาสรีรวิทยา และ ²ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

A Preliminary Study of Ventilatory Responses during Maximal Exercise in Healthy Thais

Tichanon Promsrisuk¹, Wilaiwan Khrisanapant¹, Orapin Pasurivong¹, Wachara Boonsawat², Boonsong Patjanasootorn², Burabha Pussadhamma², Nuttha Muangritdech¹, Jiraporn Khaengkhan¹, Puttapol Chanchalad¹
Department of ¹Physiology, and ²Medicine, Faculty of Medicine, Khon Kaen University

หลักการและวัตถุประสงค์: การทดสอบการทำงานของหัวใจ หลอดเลือด และปอด ขณะออกกำลังกายใช้ในการประเมินความสามารถในการทำงานของระบบหัวใจ หลอดเลือด และระบบหายใจในการออกกำลังกายสูงสุด และใช้ในการวินิจฉัย พยากรณ์โรค ในผู้ป่วยหัวใจและ หลอดเลือด และผู้ป่วยโรคระบบทางเดินหายใจ การประเมินรูปแบบการหายใจขณะออกกำลังกายสูงสุดในผู้ป่วยมีข้อจำกัด เพราะยังไม่มีการศึกษาถึงการตอบสนองของการระบายอากาศขณะออกกำลังกายสูงสุดในคนไทยสุขภาพดี การศึกษานี้จึงมีวัตถุประสงค์เพื่อประเมินการตอบสนองของการระบายอากาศขณะออกกำลังกายสูงสุด และเปรียบเทียบการตอบสนองดังกล่าวระหว่างเพศชายกับหญิงในประชากรไทยสุขภาพดี

วิธีการศึกษา: อาสาสมัครสุขภาพดี 30 ราย (เพศชาย 15 ราย อายุเฉลี่ย 27±5 ปี และหญิง 15 ราย อายุเฉลี่ย 27±3 ปี) ได้รับการทดสอบการทำงานของหัวใจ หลอดเลือด และปอด ขณะออกกำลังกาย โดยมีการปรับเพิ่มความหนักของการออกกำลังกายจนกระทั่งอาสาสมัครไม่สามารถทำการทดสอบต่อไปได้

ผลการศึกษา: อาสาสมัครทุกคนมีสุขภาพดี โดยที่น้ำหนักส่วนสูง ในเพศชายมากกว่าหญิง (p<0.001) งานสูงสุด ปริมาตรอากาศทั้งหมดที่หายใจเข้าหรือออกเต็มที่ใน 1 นาที ปริมาตรการระบายอากาศใน 1 นาที และปริมาตรอากาศที่หายใจเข้าออกแต่ละครั้ง ขณะออกกำลังกายสูงสุดในเพศชายมากกว่าหญิง (205 vs 111 วัตต์, 149.5 vs 107.2 ลิตร/นาที, 96.1 vs 54.8 ลิตร/นาที; p<0.001 และ 2.0 vs 1.3 ลิตร; p<0.01) นอกจากนี้ ความถี่ของการหายใจ ปริมาตรอากาศที่หายใจเข้าออกแต่ละครั้ง และปริมาตรการระบายอากาศใน

Background and objectives: Cardiopulmonary exercise testing (CPET) evaluates the ability of cardiovascular and respiratory systems in maximal exercise. It is used for the diagnosis and prognosis of cardiovascular and pulmonary disease patients. Assessment of the breathing pattern at maximal exercise in patients is limited because the range of ventilatory responses at maximal exercise in healthy Thai is unknown. This study aimed to evaluate the ventilatory response to maximal exercise and to compare the differences in these responses between genders.

Methods: The maximal cardiopulmonary responses were performed in 30 healthy Thai subjects (15 males; aged 27±5 years and 15 females; aged 27±3 years) who underwent the CPET using a ramp protocol until reaching symptom limitation.

Results: All subjects had normal ranges of clinical characteristics except that weight and height in males were higher than in females (p<0.001). Maximal work rate (WR_{max}), maximal voluntary ventilation (MVV), maximal expired total ventilation (VE_{max}) and maximal tidal volume (VT_{max}) in males were significantly higher than in females (205 vs 111 W, 149.5 vs 107.2 L/min, 96.1 vs 54.8 L/min; p<0.001 and 2.0 vs 1.3 L; p<0.01). In addition, respiratory frequency (Rf), VT and VE increased as a function of WR in both genders (p<0.001). Nevertheless, the breathing reserve was not significantly different between genders.

*Corresponding author :

1 นาที เพิ่มขึ้นตามการเพิ่มของงานทั้งสองเพศ ($p < 0.001$) อย่างไรก็ตาม การหายใจสำรองไม่มีความแตกต่างกันระหว่างชายและหญิง

สรุป: การศึกษาครั้งนี้ทำให้ทราบถึงการตอบสนองของการระบายอากาศขณะการออกกำลังกายสูงสุด โดยใช้การทดสอบการทำงานของหัวใจ หลอดเลือด และปอด ขณะออกกำลังกาย ในคนไทยสุขภาพดี นอกจากนี้ยังแสดงให้เห็นว่าการตอบสนองของการระบายอากาศขณะเริ่มล้มและขณะออกกำลังกายสูงสุดในเพศชายสูงกว่าหญิง

คำสำคัญ: การตอบสนองของการระบายอากาศ การออกกำลังกายสูงสุด การทดสอบการทำงานของหัวใจ หลอดเลือด และปอด ขณะออกกำลังกาย

Conclusions: The present study provides primarily data on ventilatory responses to maximal exercise using the CPET in healthy Thais. We also demonstrated that males have ventilatory responses at an anaerobic threshold (AT) and at maximal exercise higher than those of females.

Keywords: ventilatory response, maximal exercise, cardiopulmonary exercise testing

ศรีนครินทร์เวชสาร 2557; 29 (4):370-376. ♦ Srinagarind Med J 2014; 29 (4):370-376.

Introduction

It has been well known that the CPET is generally used to evaluate responses of various organs including cardiovascular, pulmonary, circulatory, neural and musculoskeletal systems to sub-maximal and maximal exercise¹⁻³. In addition, it is being used for diagnosis and prognosis patients with cardiovascular and pulmonary diseases⁴. These responses are then compared to previously established "normal" values in order that judgment regarding limitation of exercise by cardiac, respiratory, or other factors could be offered⁵. Ventilatory responses to exercise up to a maximal level have been found to be useful in assessing the presence and severity of both heart and lung diseases⁶. Most studies of "normal" responses have focused on the prediction of power and oxygen uptake at maximal exercise, as well as the ventilatory and heart rate responses to exercise⁷⁻¹⁰. The general pattern of the expected changes in ventilatory responses, namely \dot{V}_E , VT and Rf are well known,¹⁰⁻¹³ but the range of individual responses that may occur at maximal exercise have not been studied thoroughly in Thai subjects. This lack of information limits the physicians to draw conclusions from ventilatory data at maximal exercise.

\dot{V}_E max is similar for leg cycling, treadmill walking and running but is less for arm cycling because the

maximal metabolic rate is lower when smaller muscle groups are used^{14, 15}. Moreover, several studies have reported \dot{V}_E max in males being higher than in females^{3,5,16,17}.

The difference between the measured maximal voluntary ventilation (MVV) and \dot{V}_E max during exercise is used as a measure of the ventilatory or breathing reserve (BR)¹⁸. The BR is usually reduced in patients with moderate to severe restrictive or obstructive lung disease¹⁹. A comparison between males and females reveals that males have higher BR than females⁵. On the contrary, Mohammad and coworkers found that BR was not different between genders³.

Therefore, the aims of this study were to evaluate the ventilatory responses to maximal exercise in healthy Thais and to compare differences in those responses between genders.

Methods

Study design and Population

In this study, the design was analytical and descriptive. The subjects in the present study were recruited from the healthy population in the Khon Kaen province of Thailand. Thirty of them (15 males and 15 females) aged between 20-40 years were participated. Number of subjects was calculated according to a previous study done by Fairbairn et al.²⁰ They were

healthy with BMI between 18.5 to 24.9 kg/m². Those having history of regular alcohol drinking, smoking, cardiovascular, neuromuscular, arthritic, pulmonary diseases, severe microvascular diseases, diabetes mellitus, hypertension or other debilitating diseases were not included in this study. Physical examination and health questionnaires regarding health were obtained. Additionally, a written informed consent was obtained from all subjects after a full explanation of the procedures and risks. This study was approved by the Human Research Ethics Committee, Khon Kaen University (HE561453).

Clinical and Anthropometric Characteristics

Height and weight were measured for each participant according to the WHO guidelines²¹. Participants wore light clothing without shoes. Weight was determined using a digital scale to the nearest tenth. Height was measured standing with feet together and arms relaxed at the sides. The BMI was calculated as weight (kg) divided by height (m²).

Cardiopulmonary Exercise Testing

Each subject performed an incremental exercise test on a treadmill (Stationary CPET, Cosmed, Quark CPET). The protocol for CPET was calculated based on age, weight, height, gender and WR according to the formula of Porszasz and colleagues²². Furthermore, they had to spend a few hours to familiarize with equipments and the CPET protocol in advance. The protocol included a 2-min rest period in the standing position on a treadmill, 3-min warm-up by beginning to walk at 0.9 km/h, followed by increases in speed rate and inclination every 1 min until exhaustion and, finally, 3-min recovery at a speed of 0.9 km/h. All tests were performed in room air (25°C) according to current guidelines for exercise testing, with continuous monitoring of ECG, blood pressure and oxygen saturation². The test could be interrupted either by the subjects, because of dyspnea, leg fatigue or disabling symptoms, or by the investigator, for safety reasons.

The criteria for reaching maximal exercise were three or more of the followings: reaching a plateau in $\dot{V}O_2$, maximum heart rate (HR) more than 90% of the predicted value for that age (220-age), RER more than

1.15 (although RER values are not exactly indicative of maximum capacity), subject requested stopping because of severe fatigue or dyspnea, and reaching 18 points or more of the RPE scales (Borg's scales)²³.

Statistical Analysis

Data were expressed as mean(SD). The Stata 10 Statistical software was used to perform the statistical analysis. Unpaired t-test was used to compare differences in characteristics, lung function and all parameters between male and female. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was used when data deviate from normality. A value of p<0.05 was taken to be the threshold of statistical significance.

Results

The average age was 27 ± 5 in females and 27 ± 3 years in males. Weight and height were significantly higher in males comparing to those of females (64.6 ± 8 vs. 53.0 ± 5.5 kg. and 174.0 ± 10.0 vs. 159.2 ± 6.6 cm.; p<0.001). Nonetheless, BMI were comparable (21.3 ± 2.0 vs. 20.9 ± 2.0 kg/m²). SBP, DBP, MAP, HR and Rf in males and females were within normal ranges (Data not shown).

We observed normal pulmonary function expressed as %predicted in both males and females. Furthermore, there were no significant differences in pulmonary function between genders (Table 1).

Table 2 and Fig. 1 summarize ventilatory responses during the cardiopulmonary exercise testing. WRmax was 91.5% predicted in males and slightly lower, e.g. 84.7%

Table 1 Pulmonary functions of the studied population.

	Males (n=15)	Females (n=15)
FVC	96.3 (14.2)	102.1 (10.5)
FEV ₁	100.7 (13.7)	100.3 (10.0)
FEV ₁ /FVC	100.7 (5.4)	98.6 (5.6)
PEF	88.6 (18.7)	89.1 (14.5)
FEF25-75%	97.2 (25.8)	94.3 (17.3)

Values are mean(SD) expressed as % predicted value. FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; PEF, peak expiratory flow; FEF, forced expiratory flow between 25 and 75% of forced vital capacity.

predicted in females ($p < 0.001$). Besides, $\dot{V}E$ and VT but not Rf at the AT and at maximal exercise of males were higher than those of females, e.g. $\dot{V}E$ 1.5 and 1.75 folds; VT 1.7 and 1.5 folds ($p < 0.001$) (Table 2). MVV in males were significantly 1.39 folds higher than in females ($p < 0.001$). The mean BR of males and females were similar, 53.4 and 52.4 L/min. There was no difference in BR between male and female (Table 2). The WRmax was significantly higher in males than in females ($p < 0.001$) (Fig. 1A).

Fig. 1B, 1C and 1D depict the relationships between ventilatory responses and WR in both genders. It was found that Rf, VT and $\dot{V}E$ has positive correlations with WR (males, $r = 0.8138$, $r = 0.6745$ and $r = 0.8524$, $p < 0.001$; females, $r = 0.6230$, $r = 0.7196$ and $r = 0.8647$; $p < 0.001$). Similarly, Fig. 1E, 1F and 1G show positive relationships between Rf, VT and $\dot{V}E$ to $\dot{V}O_2$ in both genders (males, $r = 0.7508$, $r = 0.8696$ and $r = 0.9358$, $p < 0.001$; females, $r = 0.5551$, $r = 0.8222$ and $r = 0.8945$; $p < 0.001$).

Besides, at a given WR, Rf (30 vs 22 /min) and $\dot{V}E$ (28 vs 23 L/min) responses to WR up to 150 watts in females were greater while VT (0.9 vs 1.2 L) lower than those of males ($p < 0.001$).

Discussion

This study presents preliminary normative values for ventilatory responses to incremental exercise testing on a treadmill. The pulmonary function (Table 1) of our population sample was within the reported normal ranges, suggesting that the samples used in the present study are healthy population.

To our knowledge, the present study is the first to report higher WRmax, max, VTmax and MVV in males compared to females, and ventilatory responses were closely related to the amount of exercise (WR and $\dot{V}O_2$) in healthy Thai population. Apparently, Rf and $\dot{V}E$ responses to WR in females were greater but VT lower than those of males. In addition, this study observed no significant difference in BR between genders.

In both genders, WRmax were similar to estimates of the Chinese but approximately 9% (males) and 15%

(females) less than those of Caucasians^{17, 22}. Previous studies have demonstrated that the WRmax of exercise depend on gender, age, body size and ethnicity^{10, 23-25}. Thai population differs from the Caucasians, in their body structure, nutrition, physical activity, environment, and socioeconomic factors²³. Thus, the difference in WRmax between Thais and Caucasians could be due to differences in those factors mentioned above.

The previous study suggests that VTmax could be used to speculate the ventilatory capacity and other resting pulmonary function measurements. Obviously, the VTmax depend on height, age, and gender¹⁸. The findings that VTmax and $\dot{V}E$ max in males were higher than in females are in agreement with several studies reported earlier^{3, 5, 16, 17}. Several studies have demonstrated that age, gender, body size, physical activities, and exercise mode influence ventilatory efficiency^{6, 16, 22}. It is likely that a body size, lung volumes, muscle mass and physical activities are attributable to higher VTmax and $\dot{V}E$ max in males^{3, 5, 16, 17}.

The values for assessing $\dot{V}E$ at the end of exercise have been suggested. The first method is to calculate "breathing reserve" at the end of exercise (BR = MVV - $\dot{V}E$ max). Any values less than 11 L/min are considered to be abnormal²⁶. We used the same method to calculate the BR in our population. Regardless of genders, all subjects had BR of higher than 11 L/min at the end of exercise. The observation that no influence of genders on BR is consistent with studies in Iranian³. In their study there were 20 males and 14 females recruited. On the contrary, studies in larger population by Ong et al.¹⁷ and Blackie et al.⁵ have demonstrated that the BR at the end of exercise in males was higher than that of females. We suggest that our study had small number of sample population. A further study in a greater sample size is crucial so that a concrete conclusion could be made.

MVV provides an estimate of the ventilatory reserves available to meet the physiologic demands of exercise²⁷. Wasserman and colleagues have recommended that the indirect MVV ($FEV_1 \times 40$) is used in calculating BR¹⁸. Normal values of MVV depend on gender, lung size, height, age and race²⁸. This is consistent with our study

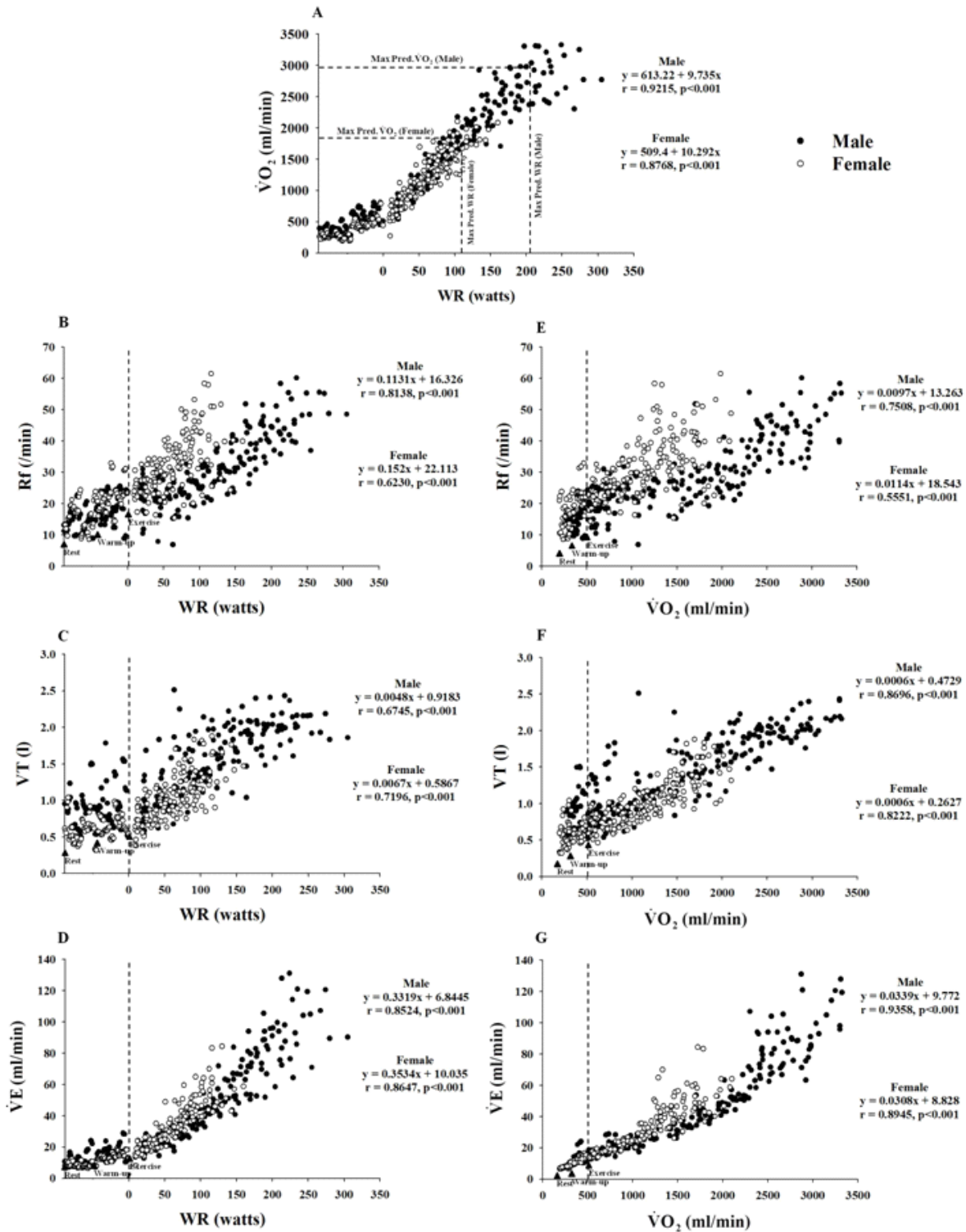


Figure 1 A: Relationship between oxygen uptake ($\dot{V}O_2$) and work rate (WR). B-D: Relationships between respiratory frequency (Rf), tidal volume (VT), expired total ventilation ($\dot{V}E$) and WR. E-G: Relationships between respiratory frequency (Rf), tidal volume (VT), expired total ventilation ($\dot{V}E$) and $\dot{V}O_2$.

Table 2 Ventilatory responses data during cardiopulmonary exercise testing

	Males (n=15)	Females (n=15)
WRmax, watts	205 (39)	111 (18)***
WRmax pred, watts	224 (28)	131 (19)**
WRmax, %pred	91.5	84.7
\dot{V}_E , 1/min (rest, AT, max ex)	11.5 (4.1), 44.5 (6.9), 96.1 (18.0)	9.2 (3.4), 30.1 (6.8)***, 54.8 (10.2)***
VT, 1 (rest, AT, max ex)	0.8 (0.3), 1.7 (0.3), 2.0 (0.3)	0.6 (0.2), 1.0 (0.2)***, 1.3 (0.3)***
Rf, /min (rest, AT, max ex)	14 (4), 26.5 (5.5), 47.7 (6.1)	16 (5), 30.8 (6.5), 42.1 (8.2)
MVV, 1/min	149.5 (21.8)	107.2 (16.2)***
MVV pred, 1/min	104.2 (10.7)	94.0 (10.1)*
Exercise breathing reserve, 1/min	53.4 (27.7)	52.4 (15.4)

WRmax, maximum work rate; WRmax pred, maximum work rate predicted; \dot{V}_E , expired total ventilation; VT, tidal volume; Rf, respiratory frequency; MVV, maximal voluntary ventilation; AT, anaerobic threshold; max ex, maximum of exercise. Values are mean(SD). **p<0.01, ***p<0.001 male versus female

which found that MVV in males were higher than in females. Similarly, former studies have shown that MVV in males was greater than in females^{25, 27}.

Hey et al.¹³ have recommended that VT related to \dot{V}_E is used to analyze the breathing pattern. We found that at low exercise intensity, the increase in \dot{V}_E is accomplished primarily by an increase VT whereas at high exercise intensity further increases in \dot{V}_E are accomplished primarily by increasing Rf. This is in line with the study of Wasserman et al.¹⁸.

We demonstrate the positive correlations of ventilatory responses and intensity of exercise in our study. Our finding that increases in ventilatory responses were linearly correlated with the increasing WR and $\dot{V}O_2$ in both males and females are consistent with studies reported previously^{5, 6}. It is reasonable that ventilation should be more closely related to WR and $\dot{V}O_2$ as ventilation is primarily driven by metabolic needs⁵. We also observed that Rf and \dot{V}_E responses to WR up to 150 watts in females were relatively greater while VT was lower than those of males. The mechanisms responsible for this observation need to be explored in the future.

Conclusions

The present study derives ventilatory responses for CPET in healthy Thai population. Thai males have

ventilatory responses to incremental exercise higher than those of females being consistent with other ethnics; Chinese, Brazil, British and Iranian. A further study in a large population is required before normal values for CPET is established.

Acknowledgement

This study was supported by the Invitation Research Grant (I56342), the Faculty of Medicine, Khon Kaen University, Thailand. Mr. Tichanon Promsrisuk was supported by a Scholarship for Promotion of Education for Graduate Students in Medical Sciences, Faculty of Medicine, Khon Kaen University.

References

1. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Postgrad Med J* 2007;83:675-82.
2. American Thoracic Society/American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211-277.
3. Mohammad MM, Dadashpour S Adimi P. Predicted Values of Cardiopulmonary Exercise Testing in Healthy Individuals (A Pilot Study) *Tanaffos* 2012;11:18-25.
4. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191-225.

5. Blackie SP, Fairbairn MS, McElvaney NG, Wilcox PG, Morrison NJ, Pardy RL. Normal values and ranges for ventilation and breathing pattern at maximal exercise. *Chest* 1991;100:136-42.
6. 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.
7. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85:546-62.
8. Drinkwater BL, Horvath SM, Wells CL. Aerobic power of females, ages 10 to 68. *J Gerontol* 1975;30:385-94.
9. Froelicher VF, Jr., Allen M, Lancaster MC. Maximal treadmill testing of normal USAF aircrewmembers. *Aerosp Med* 1974;45:310-5.
10. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;131:700-8.
11. Dempsey JA, Vidruk EH, Mastenbrook SM. Pulmonary control systems in exercise. *Fed Proc* 1980;39:1498-505.
12. Gallagher CG, Brown E, Younes M. Breathing pattern during maximal exercise and during submaximal exercise with hypercapnia. *J Appl Physiol* (1985) 1987;63:238-44.
13. Hey EN, Lloyd BB, Cunningham DJ, Jukes MG, Bolton DP. Effects of various respiratory stimuli on the depth and frequency of breathing in man. *Respir Physiol* 1966;1:193-205.
14. Davis JA, Vodak P, Wilmore JH, Vodak J, Kurtz P. Anaerobic threshold and maximal aerobic power for three modes of exercise. *J Appl Physiol* 1976;41:544-50.
15. Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 1969;26:31-7.
16. Herdy AH, Uhlendorf D. Reference values for cardiopulmonary exercise testing for sedentary and active men and women. *Arq Bras Cardiol* 2011;96:54-9.
17. Ong KC, Loo CM, Ong YY, Chan SP, Earnest A, Saw SM. Predictive values for cardiopulmonary exercise testing in sedentary Chinese adults. *Respirology* 2002;7:225-31.
18. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, et al., Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. 4 ed. 2005.
19. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:9-18.
20. Fairbairn MS, Blackie SP, McElvaney NG, Wiggs BR, Pare PD, Pardy RL. Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. *Chest* 1994;105:1365-9.
21. WHO. Waist circumference and waist-hip ratio: report of a WHO expert consultation WHO technical report series. . Geneva: World Health Organization 2008;34.
22. Porszasz J, Casaburi R, Somfay A, Woodhouse LJ, Whipp BJ. A treadmill ramp protocol using simultaneous changes in speed and grade. *Med Sci Sports Exerc* 2003;35:1596-603.
23. Nogueira FS, Pompeu FA. [Maximal workload prediction models in the clinical cardio-pulmonary effort test]. *Arq Bras Cardiol* 2006;87:137-45.
24. John N, Thangakunam B, Devasahayam AJ, Peravali V, Christopher DJ. Maximal oxygen uptake is lower for a healthy Indian population compared to white populations. *J Cardiopulm Rehabil Prev* 2011;31:322-7.
25. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. *Eur Respir J* 1999;14:1304-13.
26. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984;129:S49-55.
27. Dillard TA, Hnatiuk OW, McCumber TR. Maximum voluntary ventilation. Spirometric determinants in chronic obstructive pulmonary disease patients and normal subjects. *Am Rev Respir Dis* 1993;147:870-5.
28. Feher JJ. Quantitative Human Physiology: An Introduction. 2012.

