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Value of cardiopulmonary exercise testing in the diagnosis of coronary artery disease

Berna AKINCI ÖZYÜREK¹
Şerife SAVAŞ BOZBAŞ²
Alp AYDINALP³
Hüseyin BOZBAŞ⁴
Gaye ULUBAY²

¹ Clinic of Chest Diseases, Ankara Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Ankara, Turkey

¹ Ankara Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Ankara, Türkiye

² Department of Chest Diseases, Ankara Hospital, Baskent Hospital, Ankara, Turkey

² Başkent Üniversitesi Ankara Hastanesi, Göğüs Hastalıkları Anabilim Dalı, Ankara, Türkiye

³ Department of Cardiology, Ankara Hospital, Baskent University, Ankara, Turkey

³ Başkent Üniversitesi Ankara Hastanesi, Kardiyoloji Anabilim Dalı, Ankara, Türkiye

⁴ Clinic of Cardiology, Ankara Güven Hospital, Ankara, Turkey

⁴ Ankara Güven Hastanesi, Kardiyoloji Kliniği, Ankara, Türkiye

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Yazışma Adresi (Address for Correspondence)

Dr. Berna AKINCI ÖZYÜREK
Ankara Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi,
Göğüs Hastalıkları Kliniği, ANKARA - TÜRKİYE
e-mail: drberna_1982@yahoo.com

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SUMMARY

Value of cardiopulmonary exercise testing in the diagnosis of coronary artery disease

Introduction: Respiratory and cardiac functions in association with skeletal and neurophysiologic systems can be evaluated with cardiopulmonary exercise testing (CPET). Compared to treadmill exercise test, CPET provides more comprehensive data about the hemodynamic response to exercise.

Materials and Methods: We aimed to evaluate the relationship with CPET findings and coronary lesions identified on angiography in patients with angina pectoris who underwent treadmill exercise, CPET and coronary angiography (CAG). By this way we sought to examine the CPET parameters that might be predictive for coronary artery disease (CAD) before diagnostic exercise test results and ischemia symptoms develop. Thirty patients in whom CAG was planned because of symptoms and exercise test results were enrolled in the study. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), maximum work rate (WR), $\Delta VO_2/\Delta WR$ and O_2 pulse (VO_2/HR) values were calculated. Significant CAD was defined as $\geq 50\%$ narrowing in at least one of the coronary arteries.

Results: The mean age was 60.4 ± 8.9 years ve 21 (65.6%) of subjects were male. On CAG, CAD was detected in 19 (59.4%) patients. Maximum heart rate, heart rate reserve (HRR), VE/VCO_2 measured at anaerobic threshold

(AT) and VO_2 (mL/kg/min) were significantly differed in patients with CAD than those without ($p= 0.031$; $p= 0.041$; $p= 0.028$; $p= 0.03$ respectively). Peak VO_2 , VO_2/WR and O_2 pulse values were higher in patients with normal angiographic results than those with CAD but the difference did not reach to statistical significance.

Conclusion: The findings of our study indicate that among CPET parameters AT VE/VCO_2 , $ATVO_2$ (mL/kg/dk) and HRR can have predictive value in the diagnosis of CAD. We think that these parameters might be used in the evaluation of patients with angina and dyspnea suspected of CAD. In conclusion parameters obtained during the test that are not influenced by patient's effort might increase the value of CPET in the diagnosis CAD.

Key words: Coronary artery disease; cardiopulmonary exercise testing; heart rate

ÖZET

Kardiyopulmoner egzersiz testlerinin koroner arter hastalığındaki tanısal değeri

Giriş: Kardiyopulmoner egzersiz testi (KPET) solunumsal ve kardiyak işlevlerle birlikte kas-iskelet sistemi ve nörofizyolojik sistemlerin değerlendirilmesini sağlayan bir yöntemdir. KPET egzersize hemodinamik yanıtı klasik efor testine kıyasla detaylı olarak değerlendirilmizi sağlar.

Materyal ve Metod: Çalışmamızda göğüs ağrısı tanımlayan, efor testi yapılan ve koroner anjiyografi (KAG) planlanan hastalara KPET yapılarak, KPET bulguları ile KAG'da saptanan lezyon yaygınlığı arasındaki ilişkiyi araştırdık. Böylece efor testinde tanısal EKG bulguları ve iskemiyle ilişkili semptomlar gelişmesini beklemeden, KPET ile koroner arter hastalığı (KAH) için tanısal olan parametreleri belirlemeyi amaçladık. Çalışmamıza semptomları ve efor testi sonuçları ile KAG planlanan 30 hasta dahil edildi. Oksijen kullanımı (VO_2), karbondioksit üretimi (VCO_2), dakika ventilasyonu (VE), maksimum ulaşılan iş yükü (WR), $\Delta VO_2/\Delta WR$ ve O_2 pulse (VO_2/HR) değerleri hesaplandı. Koroner arterlerden herhangi birinde \geq %50 darlığın saptanması anlamlı koroner arter hastalığı kabul edildi.

Bulgular: Hastaların ortalama yaşı 60.4 ± 8.9 yıl ve 21 (%65.6)'i erkekti. Koroner anjiyografi ile 19 (%59.4) hastada koroner arterlerde stenoz saptandı. KAH saptanan grupta maksimum kalp hızı, kalp hızı rezervi (HRR), anaerobik eşik (AT)'te ölçülen VE/VCO_2 ve VO_2 (mL/kg/dk) KAH saptanmayan gruba göre anlamlı farklıydı ($p < 0.05$). KAH saptanmayan hastalarda VO_2 pik, VO_2/WR ve O_2 pulse değerleri KAH saptanan gruba göre yüksek saptandı, ancak istatistiksel olarak anlamlı bulunmadı ($p > 0.05$).

Sonuç: Çalışmamız sonucunda AT, VE/VCO_2 , $ATVO_2$ (mL/kg/dk), maksimum HR ve HRR'nin KAH tanısını destekleyen önemli parametreler olduğu saptandı. Bu nedenle dispne ve göğüs ağrısı etiyojisine yönelik değerlendirilen hastalarda bu parametrelerin KAH için tanısal olabileceği düşüncesindeyiz. Sonuç olarak hasta eforundan etkilenmeyen ve tetkik sırasında görüntülenebilen parametreler KPET'in KAH tanısında kullanımını artıracaktır.

Anahtar kelimeler: Koroner arter hastalığı; kardiyopulmoner egzersiz testi; kalp hızı

INTRODUCTION

Cardiopulmonary exercise testing (CPET) is a useful and detailed test in the evaluation of respiratory, cardiovascular, skeletal and neurophysiologic systems. CPET is especially used to assess cardiac functions and prognosis of heart failure and determine the indication of cardiac transplantation in cardiology (1).

CPET for coronary artery disease (CAD) assessment is an area of growing clinical interest in which different parameters provide both diagnostic and prognostic insight for evaluation and management (2). However ECG stress test (classical effort test) is preferred in clinical practice because need for calibration before each test, requirement of experienced and educated personnel and the increased cost of equipment put CPET on the back burner (3).

Myocardial ischemia with increased workload in the classical effort test can manifest itself with ST changes, chest pain, ventricular arrhythmias, or falls in blood

pressure. However, these findings may not be found in all cases. CPET allows us to evaluate the hemodynamic response to the exercise in more detailed manner compared to the classic effort test.

Oxygen uptake (VO_2), carbon dioxide production (VCO_2), anaerobic threshold (AT), O_2 pulse, VO_2/WR and respiratory equivalent during anaerobic threshold (VE/VCO_2) can be abnormal in cardiovascular diseases (3). Gas analysis can detect myocardial ischemia during exercise with reduced pulse volume and cardiac out-put before the development of ST segment changes or chest pain (3).

In the present study CPET was performed to subjects with chest pain in addition to effort test, and coronary angiography (CAG), and we investigated the relationship between CPET findings and CAG findings detected on coronary angiography. Moreover we aimed to determine the diagnostic parameters for coronary artery disease with CPET in subjects before the development of diagnostic ECG findings and ischemia related symptoms during effort test.

MATERIALS and METHODS

This study (project numbered KA04/198) was conducted with the approval of the ethics committee of Başkent University Medical Faculty Research Council.

A written informed consent form was obtained from all subjects before participating in the study.

Patients with chest pain, ST segment changes during the effort test, and scheduled for coronary angiography were included. Thirty patients who underwent CPET before coronary angiography were evaluated. Patients with acute coronary syndrome, newly diagnosed myocardial infarction (< 2 months), congestive heart failure, severe valvular disease, diabetes mellitus requiring insulin use, and orthopedic problems that would limit exercise were excluded from the study.

Cardiopulmonary Exercise Testing

The symptom-limited cardiopulmonary exercise test (Ergo-metrics 900, SensorMedics™, Bilthoven, The Netherlands) was performed using the bicycle ergometer. All patients were instructed not to eat at least two hours before the test, and not to drink tea, coffee, cola drinks during that time.

Cardiopulmonary exercise tests were conducted at the same time of day after lunch. Calibration with two standard gas mixtures (26% oxygen + balanced N₂, 4% carbon dioxide + 16% oxygen + balanced N₂) before each testing was performed.

VO₂, VCO₂ and minute ventilation (VE), were evaluated by using gas analyzers and the face mask (Rudolph Face Mask for Exercise Testing™; Hans Rudolph Inc., Kansas City, MO).

All patients performed a 3-minute baseline period and a 3-minute warm-up period (warm-up, 0W, 60 rpm) followed by an incremental exercise test with an increased workload of 15 watt/min (4). During CPET, patients were monitored with 12-channel ECG, heart rate, oxygen saturation using a pulse oximeter (via a finger probe- NONIN 8600 pulse oximeter™, Plymouth, Minnesota USA). Blood pressure was measured and recorded manually every two minutes.

The collected data was automatically recorded (Desktop Diagnostics/CPX™; Medical Graphics Corporation, St. Paul, Minn.). The maximum workload

was considered the highest workload that patients could tolerate for at least 20-30 seconds. Anaerobic threshold was determined by V-slope method (5). The peak VO₂ was obtained by calculating the average of the values obtained in the last 30 seconds of the incremental exercise test.

VO₂/WR and O₂ pulse (VO₂/HR) values were calculated at maximum exercise.

Effort Test

The effort test was performed by using the Bruce protocol. The target heart rate was calculated as 220-age (years). 85% of this value was recorded as a submaximal target. Typical chest pain during the test, 1 mm or more subduction after 80 ms of J junction in two consecutive ST segments, 10 mmHg or more decrease in systolic blood pressure, and ST segment elevation were evaluated as positive effort test criteria. During and after the test, symptoms, heart rate and blood pressure were recorded, and continuous electrocardiographic monitoring was performed during the test and during the recovery period.

Coronary Angiography

Coronary angiography was performed through the right femoral artery after appropriate preliminary preparation and premedication. With the Judkins technique, selective coronary angiographic images were obtained in right and left oblique positions. Angiograms were evaluated by two experienced cardiologists. Each segment was numerically evaluated according to the percentage reduction in lumen diameter based on the nearest proximal intact coronary artery segment. Significant coronary artery disease was accepted in the presence of a ≥ 50% stenosis in any of the coronary arteries.

Statistical Analysis

Statistical analysis was performed using the Windows SPSS version 10.0 (Statistical Package for the Social Sciences, version 10.0, SPSS Inc, Chicago, IL, USA). The data were expressed as mean ± standard deviation or percentage. Chi-square test or t-test were used in the comparison of the variables between groups. The relationship between variables was evaluated by Spearman rank correlation or Pearson correlation test. P value < 0.05 was considered as significant.

RESULTS

Thirty patients with chest pain and positive effort test (ST segment change or chest pain during the test) who were planned for coronary angiography were included to the study. The mean age of the patients was 60.4 ± 8.9 years and 21 (65.6%) were male. The demographics, laboratory results and pulmonary function test parameters of the patients are depicted in Table 1. Complaints of patients were listed in Table 2. Twenty (62.5%) patients reached the maximum heart rate and 22 (73%) patients had ST segment depression during effort test. During or after the test 18 (56.3%) patients reported symptoms that could indicate coronary artery disease. Results of coronary angiography performed after impaired effort test were evaluated and 14 (46%) patients had stenosis in coro-

nary arteries. Based on the results of effort test and symptoms CPET was performed before CAG. No complications were seen during and after CPET. The CPET parameters of the patients are summarized in Table 3.

Results of coronary angiography performed after CPET were evaluated and 19 (59.4%) patients had stenosis in coronary arteries. Grade of coronary artery stenosis is demonstrated in Table 4. CPET parameters of patients with and without CAD were compared. Significant differences were found between patients with and without CAD in terms of maximum heart rate, heart rate reserve (HRR), VE/VCO_2 and VO_2 (mL/kg/min) (Table 5). Peak VO_2 value, VO_2/WR and O_2 pulse were found to be higher in patients without CAD than patients with CAD, but not at the level of statistical significance (Table 5).

Table 1. Demographic, laboratory and pulmonary function test parameters of study population

n= 30	
Demographics	
Age (years)	60.3 \pm 8.7
Gender (female/male)	9/21
BMI (kg/m ²)	26.6 \pm 4.9
Smoking history, n (%)	19 (63.3)
Cumulative smoking exposure (packet/years)	30.4 \pm 21.6
Laboratory results	
Hemoglobin (g/dL)	14.1 \pm 1.7
Leukocytes (10 ³ /uL)	7.1 \pm 2.0
CRP (mg/L)	4.0 \pm 4.3
Sedimentation (mm/hr)	9.9 \pm 9.2
Pulmonary function test parameters	
FVC (pred %)	98.6 \pm 14.0
FEV ₁ (pred %)	92.8 \pm 17.9
FEV ₁ /FVC (%)	74.5 \pm 10.6
FEF ₂₅₋₇₅ (pred %)	70.3 \pm 32.6
Data are expressed as the mean \pm standard deviation, the median (interquartile range), or frequency counts (percentages), as appropriate. BMI: Body mass index, CRP: C-reactive protein; FEF ₂₅₋₇₅ : Forced expiratory flow at 25-75%; FEV ₁ : Forced expiratory volume at first second; FVC: Forced vital capacity.	

Table 2. Symptoms of study population

n= 30	
Symptoms	
Chest pain, n (%)	15 (50.0)
Chest pain and exertional dyspnea n (%)	12 (40.0)
Chest pain and palpitation n (%)	2 (6.7)
Chest pain and syncope n (%)	1 (3.3)

Table 3. Cardiopulmonary exercise testing (CPET) parameters of study population

n= 30	
CPET parameters	
Resting VO_2 (mL/kg/min)	4.4 \pm 0.9
Warmup VO_2 (mL/kg/min)	11.1 \pm 1.9
Peak VO_2 (mL/kg/min)	20.3 \pm 4.5
Mean VO_2 (%)	82.8 \pm 18.1
AT VO_2 (mL/kg/min)	14.5 \pm 3.9
AT VE/VCO_2	30.7 \pm 5.1
HR maximum (beats/min)	140.9 \pm 19.6
WR maximum (watt)	88.6 \pm 30.0
VE (BTPS)	59.3 \pm 16.8
Exercise duration (min)	6.6 \pm 2.6
VO_2/WR	8.5 \pm 2.2
Oxygen pulse	10.9 \pm 2.1
AT: Anaerobic threshold, HR: Heart rate, HRR: Heart rate reserve, VCO_2 : CO_2 production, VE: Minute ventilation, VO_2 : Oxygen uptake, WR: Work rate.	

Table 4. Grade of coronary artery stenoses detected in coronary angiography

n= 19	
Coronary artery stenosis	
Minimal CAD, n (%)	6 (31.6)
Single vessel disease, n (%)	5 (26.3)
Two-vessel disease n (%)	4 (21.1)
Three-vessel disease, n (%)	3 (15.8)
Four-vessel disease, n (%)	1 (5.3)
CAD: Coronary artery disease.	

Table 5. Comparison of CPET parameters between subjects with and without CAD.

Parameters	Subjects with CAD	Subjects without CAD	p
Peak VO ₂ (mL/kg/min)	19.8 ± 4.9	21.3 ± 3.7	0.37
AT VO ₂ AT	13.4 ± 2.6	15.7 ± 2.5	0.03
AT VE/VCO ₂	31.9 ± 4.2	28.5 ± 2.9	0.028
HR maximum (beat/min)	151.0 ± 13.2	135.1 ± 20.6	0.031
HRR	22.8 ± 16.9	9.8 ± 14.1	0.041
WR maximum (watt)	85.0 ± 33.4	95.0 ± 23.1	0.39
VO ₂ /WR	8.0 ± 2.5	9.4 ± 1.3	0.11
Oxygen pulse	10.8 ± 2.5	11.0 ± 1.2	0.89

CPET: Cardiopulmonary exercise testing, CAD: Coronary artery disease, AT: Anaerobic threshold, HR: Heart rate, HRR: Heart rate reserve, VCO₂: CO₂ production, VE: Minute ventilation, VO₂: Oxygen uptake, WR: Work rate.

Moreover AT VE/VCO₂ and peak VO₂ values were negatively correlated ($r = -0.49$ $p = 0.005$).

DISCUSSION

CPET is a noninvasive, objective assessment of the body's response to exercise and can evaluate additional components of the cardiovascular and pulmonary systems. This testing provides useful information on the functional status of patients with heart failure, chronic pulmonary disease and patients with exercise intolerance (6).

In the present study, CPET was performed before angiography and AT VE/VCO₂, AT VO₂ (mL/kg/min), maximum HR and HRR were found to be important parameters supporting diagnosis of CAD. Therefore these CPET parameters should be considered as essential parameters for the diagnosis of CAD in clinical use. Furthermore these parameters can be monitored during CPET and do not require additional calculations unlike oxygen pulse or VO₂/WR. Peak VO₂ is used for diagnosis and prognosis in heart failure and CAD (7). However peak VO₂ is affected by patient motivation and threshold values of peak VO₂ are not clear (8). In addition, subjects with cardiovascular disease do not achieve the maximal targeted values due to current illnesses. For these reasons, other parameters of CPET independent from patient effort are investigated. Corra et al. evaluated 403 patients with moderately limited functional capacity, and found that VE/VCO₂ slope was a strong independent predictor of major cardiac events. In addition, they found that mortality rates of patients with VE/VCO₂ slope of ≥ 35 were similar to the mortality rates of patients with low VO₂ levels (9).

Corra and co-workers suggested that the prognostic pre-eminence of the VE/VCO₂ slope may be linked to an underlying abnormal response to exercise and sympathetic overactivity and neurohormonal imbalance (9).

Van de Veire et al. reported that NT-pro BNP levels were an important independent predictor of VE/VCO₂ in patients with CAD (8). The present study also suggests that AT VE/VCO₂ may be used in the diagnosis of CAD as this parameter can be evaluated in subjects those can not reach the maximum exercise level and significant correlation is found between AT VE/VCO₂ and CAD. Similarly, low levels of AT VO₂ are also important predictors of CAD. Therefore, high AT VE/VCO₂ and low AT VO₂ values are important parameters in the diagnosis of CAD in patients who can not reach maximum heart rate or have typical ECG findings.

Measurement of cardiac out-put is the best index for the assessment of cardiac functions during exercise. During exercise, cardiac out-put is estimated from HR. The HR gives information about the achievement of the predicted values with age, the patient's maximal effort and the peak VO₂. The predicted maximal HR can be obtained from the formula of $210 - (\text{age} \times 0.65)$. The maximum HR should exceed 90% of the predicted value. The VO₂/WR relationship reflects the metabolic need of the exercise or the oxygen requirement of the work. The normal value is 10 mL/kg/watt. VO₂/WR decreases in heart diseases and peripheral artery diseases. Coronary artery disease is associated with an early increase in HR, a decrease in oxygen delivery, and no increase in oxygen consumption (VO₂/WR) in parallel with

increased workload as a result of unmet myocardial oxygen requirement during exercise (10). In the present study, HR was found to be significantly higher in patients with CAD than in patients without CAD, while the VO_2/WR value was found to be low. However differences in VO_2/WR did not reach statistical significance level. This might be due to the small number of patients.

HRR is interpreted as the difference between the predicted maximum heart rate according to age and the maximum heart rate that the patient achieved during the test. In healthy subjects, the difference is less than 15 beats/min. Heart rate reserve can be increased or decreased or normal in cardiac diseases. HRR is an independent risk factor for mortality in CAD. HRR is usually increased in subjects with respiratory diseases. In our study, the HRR assessed during CPET was higher in patients with CAD than patients without CAD.

CONCLUSION

ATVE/ VO_2 , AT VO_2 (mL/kg/min), maximum HR and HRR independently from subjects efforts are important parameters in the assessment of CAD. Therefore clinical use of CPET in the diagnosis of CAD will increase in near future.

CONFLICT of INTEREST

All authors have no conflict of interests.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: All of authors.

Analysis/Interpretation: All of authors.

Data Acquisition: All of authors.

Writting: BAO, ŞSB, HB

Critical Revision: BAO

Final Approval: BAO, ŞSB

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