



# Diagnostic value of the cardiopulmonary exercise test in coronary artery disease

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**Background:** Coronary angiography (CAG) is “gold standard” for the diagnosis of coronary heart disease (CHD). This study aimed to explore the diagnostic value of cardiopulmonary exercise testing (CPET) and the oxygen uptake kinetics indexes of CPET.

**Methods:** One hundred thirty-one patients with chest pain who underwent coronary angiography in the Department of Cardiology of our hospital from April to September 2021 were selected. According to the results of angiography, the patients were divided into an observation group (patients with coronary heart disease, n=80) and a control group (patients without coronary heart disease, n=75). Both groups underwent CPET before angiography. The differences of peak oxygen uptake, anaerobic threshold, peak kilogram oxygen uptake, peak oxygen pulse, maximum exercise load, maximum metabolic equivalent, and exercise time between the two groups were compared. Also, the correlation between the above indexes and the degree of coronary artery stenosis was analyzed, and the clinical value of the CPET in the diagnosis of CHD was evaluated.

**Results:** The peak oxygen uptake, anaerobic threshold, peak kilogram oxygen uptake, peak oxygen pulse, maximum exercise load, maximum metabolic equivalent, and exercise time in the observation group were lower than those in the control group ( $P<0.01$ ), and were negatively correlated with the Gensini score ( $P<0.01$ ). The area under the receiver operating characteristic (ROC) curve of the above seven indexes in the combined diagnosis of CHD was 0.974, the sensitivity was 86.40%, and the specificity was 98.50%, which was better than the clinical value of any of the above indexes alone.

**Conclusions:** CPET is an effective non-invasive examination in the diagnosis of CHD, and has a certain clinical value in the evaluation of the severity of coronary artery stenosis.

**Keywords:** Coronary heart disease (CHD); chest pain; cardiopulmonary exercise test; diagnostic value; degree of coronary artery stenosis

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## Introduction

Coronary atherosclerotic heart disease, also known as ischemic heart disease, is caused by stenosis or occlusion of a vascular cavity caused by coronary atherosclerosis, resulting in myocardial ischemia, hypoxia, or necrosis,

which is referred to as coronary heart disease (CHD). According to a report released by the International Cooperative Research on Global Disease Burden in 2017, the number of CHD patients worldwide was estimated to be 110 million, and CHD was the leading cause of death in

the world (1). It has been reported that there are 11 million people suffering from CHD in China, and the proportion of all cardiovascular disease deaths has increased from 29% to 37% (2). At the same time, the age of onset tends to be younger, and the prevalence and hospitalization rate are increasing. Therefore, CHD has gradually become a major public health problem in China, increasing the significant burden on families and society. If we could achieve early detection, diagnosis, and treatment of CHD, the survival rate and quality of life of patients would be significantly improved. Clinically, the diagnosis of CHD needs to be combined with the patient's symptoms, signs, and auxiliary examination. The typical manifestation of CHD is chest pain. Clinically, the first symptoms of CHD may only be non-specific manifestations such as palpitation, chest tightness, and shortness of breath after activity. Auxiliary examination was particularly important; the non-invasive auxiliary diagnostic examination method of CHD has been a consistent research hotspot at home and abroad. With the continuous development of science and technology and the ongoing efforts of researchers, an increasing number of auxiliary examinations have been developed for the diagnosis of CHD.

Coronary angiography (CAG) has long been used as the "gold standard" in the clinical diagnosis of CHD; however, it is expensive, invasive, and has a certain risk (mortality is 0.1%, complication is 1.8%) (3), which cannot be accepted by all patients. Making the diagnostic method of CHD more accurate, safe, non-invasive, and simple has always been the goal of research at home and abroad. Cardiopulmonary exercise testing (CPET) is different to the general exercise and static lung function tests (4), and is an objective, quantitative, continuous, and non-invasive clinical detection method. It is the only clinical examination technology that can comprehensively evaluate human multi-system function simultaneously (5-7); it can monitor the changes of full lead electrocardiogram (ECG), blood pressure and blood oxygen saturation from resting state to exercise load, as well as metabolic indexes such as pulmonary ventilation index and oxygen uptake (8). Through the comprehensive analysis of dynamic changes such as overall gas exchange, cardiac electrophysiology and hemodynamics, CPET can assess the cardiopulmonary function reserve and functional damage of patients, so as to comprehensively evaluate the circulatory system functional status of the respiratory and bone systems.

As early as the 1950s, foreign countries recognized the value of CPET and carried out in-depth research. At

present, it is widely used in the evaluation of patients with CHD, heart failure, respiratory system and other diseases, but research into the diagnosis of CHD is still lacking. In recent years, domestic researchers have gradually realized the value of CPET, and there are an increasing number of relevant studies on CPET; however, the diagnosis of CHD remains controversial. Nevertheless, a number of studies (9) have shown that CPET could identify the abnormal gas exchange and abnormal response mode in patients with CHD, so as to provide a reliable basis for the diagnosis of CHD.

The purpose of this study was to explore the value of CPET and CPET-related gas indicators in the diagnosis of CHD, and to provide more evidence for non-invasive examination methods in the diagnosis of CHD. We present the following article in accordance with the STARD reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-24/rc>).

## Methods

### General information

In this study, 155 patients with chest pain who underwent CAG in the Department of Cardiology of our hospital from April to September 2021 were included in this single-center prospective study.

The inclusion criteria were as follows: (I) patients with angina pectoris symptoms; (II) patients with no previous history of revascularization; and (III) patients who could exercise for at least 3 minutes.

The exclusion criteria were as follows: (I) patients with acute myocardial infarction (3–5 d); (II) those with uncontrolled severe arrhythmias; (III) patients with acute infective endocarditis or pericarditis, syncope, severe aortic stenosis, uncontrolled heart failure, suspected interbedded pulse aneurysm, acute pulmonary embolism, uncontrolled asthma, pulmonary edema, respiratory failure, deep venous thrombosis of lower extremities, or acute dysfunction of the non-cardiopulmonary system (e.g., renal failure, thyrotoxicosis); (IV) patients with oxygen saturation  $\leq 85\%$  at rest; (V) those with mental illnesses that lead to non-cooperation; and (VI) patients with non-controlled hypertension [ $>200/120$  mmHg (1 mmHg=0.133 kpa)].

The 155 included patients were divided into two groups: an observation group ( $\geq 50\%$  lumen stenosis of major coronary artery or branch; 80 cases) and a control group (no lumen stenosis or narrowing of major coronary artery or

branch; 75 cases). We collected the clinical information of all patients.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of the Third Hospital of Shanxi Medical University (No. YXLL-2021-006) and informed consent was taken from all the patients.

### *Coronary angiography*

All patients underwent CAG with a Siemens artisize ceiling digital subtraction angiography machine (DSA) (Berlin, Germany). CAG was performed by the interventional cardiologist, and the results were interpreted at the same time. The Judkins method was used for examination. The internationally recognized Gensini score was used to evaluate the severity of coronary artery disease: 1 point for coronary artery stenosis  $\leq 25\%$ ; 2 points for stenosis 26–50%; 4 points for stenosis 51–75%; 8 points for stenosis 76–90%; 16 points for stenosis 91–99%; and 32 points for complete occlusion. According to the importance of the location of coronary artery stenosis to myocardial blood supply, the score of each lesion location was multiplied by the corresponding coefficient, such as the left main coronary artery  $\times 5$ , the proximal segment of left anterior descending branch and the proximal segment of circumflex branch of coronary artery  $\times 2.5$ , the middle segment of left anterior descending branch  $\times 1.5$ , the distal segment of the right coronary artery, the posterolateral of the left anterior descending coronary artery, the first diagonal branch, the middle and distal segment of the circumflex branch, and the blunt marginal branch  $\times 1$ , and other sections  $\times 0.5$ . The sum of coronary artery stenosis lesions in each segment is the Gensini score; the higher the score, the more serious the lesion is.

### *CPET*

Before CAG, all patients underwent CPET using the China Madecare Cardiopulmonary Exercise Testing System. Firstly, the purpose of the examination, matters needing attention in the examination process, and the pedal speed (average 60 r/min) were introduced to the patients. The patients were familiarized with the Borg score sheet, and were instructed to wave their hand in time when discomfort occurs during exercise. ECG, blood pressure, finger pulse oxygen saturation, and other monitoring equipment were

connected, and a mask was worn in a comfortable position and ensure no air leakage. Additionally, the bicycle power supply seat was adjusted to a comfortable height. The submaximal exercise test or symptom restricted exercise test exercise programs were applied, and the target heart rate =  $(220 - \text{age}) \times 85\%$ . Before exercise, the static pulmonary function was measured, followed by resting on a power bicycle for 3 min. Next, warm-up was carried out at a constant speed of 55–65 R/min under no-load for 3 min, and then the power was increased at a speed of 10–15 W/min until the target heart rate or symptom limit was reached. Generally, the time from the increase of exercise load to the time that peak exercise should be controlled is 8–12 min (10), which is the extreme exercise period. Thereafter, the resistance was removed and the patient continued to pedal the bicycle slowly for about 5 min until it stopped, which is the recovery period. The changes in oxygen consumption, blood pressure, exercise load, pulmonary ventilation index, and ECG were continuously monitored during exercise. The test was terminated when the following conditions occurred: (I) reaching the target heart rate; (II) severe angina pectoris or acute myocardial infarction; (III) during exercise, blood pressure  $\geq 250/120$  mmHg or systolic blood pressure decreased by more than 10 mmHg, accompanied by symptoms of myocardial ischemia; (IV) low perfusion signs such as pale complexion as well as wet and cold skin; (V) symptoms such as leg pain, inability to continue the test, dyspnea, etc.; (VI) persistent ventricular tachycardia; and (VII) progressive neurological symptoms (dizziness, ataxia, etc.).

### *Observed indicator*

During CPET examination, the oxygen intake (Peak  $\text{VO}_2$ ), oxygen intake ( $\text{VO}_2/\text{kg}$ ), oxygen pulse ( $\text{O}_2/\text{HR}$ ), power Load (Load), metabolic equivalent (Mets), and exercise Time (Time) were recorded during extreme exercise. The anaerobic threshold (AT) was determined by v-slope method.

### *Statistical analysis*

SPSS23.0 software (IBM, Chicago, USA) was used for data analysis. Normally distributed quantitative data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ), and the t-test was used. Quantitative data in skewness distribution were presented as quads [M (Q1, Q3)], and the non-parameter test was used. The  $\chi^2$  test was used for fixed materials. Spearman rank correlation analysis was used for correlation

**Table 1** Comparison of clinical data between the two groups

Item	Observation group (n=80)	Control group (n=75)	Statistics	P value
Age	63.48±8.96	62.68±9.72	t=1.765	0.183
Men, n (%)	55 (68.75)	40 (53.33)	$\chi^2=2.753$	0.089
Physical index (kg/m <sup>2</sup> )	25.86±3.49	26.34±3.71	t=-1.223	0.221
Smoking, n (%)	53 (66.25)	41 (54.67)	$\chi^2=1.532$	0.223
Hypertension, n (%)	67 (83.75)	26 (34.67)	$\chi^2=23.652$	<0.001
Diabetes, n (%)	20 (25.00)	7 (9.33)	$\chi^2=7.426$	0.009
Blood lipid abnormal, n (%)	30 (37.5)	14 (18.67)	$\chi^2=9.032$	0.005
Left ventricular ejection fraction (%)	58 (54, 60)	57 (54, 59)	z=1.226	0.225
Left ventricular diastolic end diameter (cm)	4.78±0.32	4.70±0.33	t=1.652	0.112
Systolic blood pressure (mmHg)	121.05±17.53	121.49±15.44	t=-0.159	0.944
Diastolic blood pressure (mmHg)	73.96±10.21	78.26±9.88	t=-1.854	0.079
Coronary artery disease, n (%)				
None	0 (0.0)	28 (37.33)		
Single branch	22 (27.5)	18 (24.00)	U=27.682	<0.001
Double branch or three	58 (72.50)	32 (42.67)		
Static heart rate (times/min)	71.36±8.96	75.36±8.44	t=-1.968	0.063
Gensini scores	62 (46, 84)	5 (0,8)	z=-9.973	<0.00

**Table 2** Comparison of CPET-related indicators between the two groups ( $\bar{x}\pm s$ )

Group	n	Peak VO <sub>2</sub> (mL/min)	AT (mL/min)	VO <sub>2</sub> /kg [mL/(min·kg)]	O <sub>2</sub> /HR (mL/beat)	Load (W)	Mets	Time (s)
Observation group	80	1236.95±289.76	904.68±270.26	17.82±2.95	10.66±1.98	83.28±16.25	4.52±0.89	383.26±73.65
Control group	75	1785.36±321.77	1203.65±158.96	23.15±3.96	12.58±2.44	122.39±28.67	6.64±1.07	556.32±62.58

CPET, cardiopulmonary exercise testing; peak VO<sub>2</sub>, the peak oxygen uptake; AT, anaerobic threshold; VO<sub>2</sub>/kg, peak kilogram body weight oxygen uptake; O<sub>2</sub>/HR, peak oxygen uptake; Mets, metabolic equivalents.

analysis. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of CPET for CHD. P<0.05 was considered to indicate a statistically significant difference.

## Results

### Comparison of clinical data between the two groups

A total of 155 patients with chest pain were enrolled, including 80 in the observation group and 75 in the contrast group. The incidence of hypertension, diabetic disease, dyslipidemia, coronary artery disease, and Gensini score in the observation group were higher than those in the control

group (P<0.05) (Table 1).

### Comparison of CPET-related indicators

The peak oxygen uptake (peak VO<sub>2</sub>), anaerobic threshold (AT), Peak kilogram body weight oxygen uptake (VO<sub>2</sub>/kg), peak oxygen uptake (O<sub>2</sub>/HR), Load, Mets, and Time in the observation group were lower than those in the control group (P<0.01, Table 2).

### Correlation analysis between the CPET-related indexes and coronary artery Gensini score

Correlation analysis showed that the peak VO<sub>2</sub>, AT, VO<sub>2</sub>/kg,

O<sub>2</sub>/HR, Load, Mets, and Time were negatively correlated with the Gensini score ( $P < 0.01$ ), as shown in the *Table 3*.

### ROC analysis of the clinical value of CPET-related indicators in the diagnosis of CHD

The area under ROC curve of peak VO<sub>2</sub>, AT, VO<sub>2</sub>/kg, O<sub>2</sub>/HR, Load, Mets, and Time for the diagnosis of CHD were 0.843, 0.744, 0.850, 0.701, 0.763, 0.855, and 0.894, respectively, all of which were greater than 0.7, and the area under Time curve was the largest (0.894). Peak VO<sub>2</sub> had the highest sensitivity (96.90%), and O<sub>2</sub>/HR had the highest specificity (92.4%). The ROC curve volume (0.974)

**Table 3** Correlation analysis of CPET-related indicators and coronary artery Gensini score

CPET index	r	P value
Peak VO <sub>2</sub>	-0.356	0.001
AT	-0.325	0.010
VO <sub>2</sub> /kg	-0.471	<0.001
O <sub>2</sub> /HR	-0.301	0.011
Load	-0.379	0.001
Mets	-0.488	<0.001
Time	-0.360	0.003

CPET, cardiopulmonary exercise testing; peak VO<sub>2</sub>, the peak oxygen uptake; AT, anaerobic threshold; VO<sub>2</sub>/kg, peak kilogram body weight oxygen uptake; O<sub>2</sub>/HR, peak oxygen uptake; Mets, metabolic equivalents.

**Table 4** ROC analysis of clinical value of CPET in diagnosing coronary heart disease

CPET index	Area under the curve	95% CI	Sensitivity (%)	Specificity (%)	Youden index	Cut-off value
Peak VO <sub>2</sub>	0.843	0.778–0.907	96.90	59.10	0.560	1,193.5 mL/min
AT	0.744	0.662–0.827	72.30	65.20	0.375	998 mL/min
VO <sub>2</sub> /kg	0.850	0.786–0.914	95.40	62.10	0.575	16.65 mL/(min·kg)
O <sub>2</sub> /HR	0.701	0.612–0.790	41.50	92.40	0.339	13.35 mL/beat
Load	0.763	0.682–0.843	84.60	56.10	0.407	89 W
Mets	0.855	0.792–0.917	95.40	62.10	0.575	4.75
Time	0.894	0.842–0.947	92.30	75.80	0.681	458 s
Combined diagnosis of 7 indicators	0.974	0.951–0.998	86.40	98.50	0.840	

ROC, receiver operating characteristic; CPET, cardiopulmonary exercise testing; peak VO<sub>2</sub>, the peak oxygen uptake; AT, anaerobic threshold; VO<sub>2</sub>/kg, peak kilogram body weight oxygen uptake; O<sub>2</sub>/HR, peak oxygen uptake; Mets, metabolic equivalents.

of the above seven indexes was higher than the diagnostic value of any index alone, with a sensitivity of 86.40% and a specificity of 98.50% (*Table 4*).

### Discussion

During bodily movement, the heart and lung mutually cooperate to meet the increased oxygen demand of muscles. The compensatory capacity of the lung is strong, so movement is generally limited to the cardiovascular system. Coronary artery stenosis in patients with coronary heart disease leads to insufficient blood and oxygen supply to the myocardium, resulting in abnormal myocardial energy metabolism, blocked cardiac systolic function, reduced cardiac flow and reduced muscle stem capacity, resulting in changes in a series of physiological indexes such as oxygen consumption and oxygen utilization. These changes are not monitored by conventional non-invasive tests performed by Treadmill exercise test (TET); however, CPET accurately evaluates cardiac blood and oxygen supply by monitoring air exchange in the airway from a physiological perspective. In addition, some patients with early CHD that was not easily detected by TET were screened out (11,12). Studies have shown that CPET was superior to TET in the diagnosis of CHD, and the sensitivity and specificity of CPET can reach 88% and 98%, respectively (13).

Peak VO<sub>2</sub> refers to the oxygen uptake of the subject per minute in the incremental load exercise test, which cannot maintain the power to continue to increase due to various factors, and reaches the maximum exercise state. It represents the oxygen transport capacity of the circulatory

system and is an important indicator of cardiopulmonary function, but is subject to the influence of body weight, age, and gender.  $\text{VO}_2/\text{kg}$  excludes the influence of body weight on oxygen uptake and can accurately reflect cardiac function (8). AT refers to the moment when the energy generated by aerobic metabolism cannot meet the needs of the body after reaching a certain exercise intensity, and anaerobic metabolism begins to participate in energy supply. Compared with peak  $\text{VO}_2$ , AT can reflect the ability of muscle mitochondria to use oxygen (9). Peak  $\text{VO}_2$  and AT can judge the severity of cardiac function impairment and evaluate the patient's cardiac function status. Studies have shown that peak  $\text{VO}_2$  in patients with CHD is lower than that in patients without CHD (6-8). Popovic *et al.* (13) found that the more serious the coronary artery lesions were, the lower the oxygen intake was, which was consistent with the above results. The results of this study showed that peak  $\text{VO}_2$ , AT, and  $\text{VO}_2/\text{kg}$  in the observation group were all lower than those in the control group, and were negatively correlated with the Gensini scores ( $P < 0.01$ ).  $\text{O}_2/\text{HR}$  is the ratio of oxygen uptake to heart rate, which is equivalent to the product of cardiac output per stroke and the difference in oxygen content of artery-mixed venous blood. Some studies (11-14) have reported that decreased  $\text{O}_2/\text{HR}$  has diagnostic value for myocardial ischemia; the more serious myocardial ischemia is, the more obvious  $\text{O}_2/\text{HR}$  decrease is, which is due to movement

With increased load, the cardiac output of CHD patients decreases. The results of this study showed that the  $\text{O}_2/\text{HR}$  in observation group was lower than that in control group, and was negatively correlated with the Gensini score ( $P < 0.05$ ). Mets are calculated from the average oxygen intake per minute of a normal 40-year-old male weighing 70 kg at rest; i.e., one metabolic equivalent equals 3.5 mL of oxygen per kilogram of body weight per minute. Maximum exercise load and exercise time are important indicators reflecting human exercise intensity and motion tolerance (12). The results of this study showed that the Load, Mets, and Time in the observation group were lower than those in the control group, and there was a negative correlation with the Gensini score ( $P < 0.01$ ), suggesting that the more severe the coronary artery stenosis, the lower the exercise tolerance. In addition, our results also showed that the area under ROC curve for the independent diagnosis of CHD by CPET-related indexes was  $\text{Time} > \text{Mets} > \text{VO}_2/\text{kg} > \text{Peak VO}_2 > \text{Load} > \text{AT} > \text{O}_2/\text{HR}$  in descending order (0.894, 0.855, 0.850, 0.843, 0.763, 0.744, 0.701, respectively). Peak  $\text{VO}_2$

had the highest sensitivity (96.90%), but its specificity was lower (59.10%).  $\text{O}_2/\text{HR}$  had a low sensitivity (41.50%), but its specificity was the highest (92.40%), highlighting the limitations of the above indexes in diagnosing CHD alone. In this study, the above seven indicators were combined for diagnosis, and the area under the ROC curve increased to 0.974, the sensitivity was 86.40%, and the specificity was 98.50%, which was the same as those reported by Nichols *et al.* (14). We observed that the clinical value of combined diagnosis is superior to the above CPET-related indicators alone.

There were some limitations in this study that should be considered. Firstly, the selected cases were limited and need to be confirmed by large-scale and multicenter prospective studies. Also, given that some cases were coronary microcirculation lesions, this might lead to false positive CPET results. In conclusion, CPET is a non-invasive examination that has a high clinical value in the diagnosis of CHD, and could indirectly reflect the degree of coronary artery stenosis. Moreover, it is inexpensive and easy to operate, and could be widely used in clinical practice.

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## Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-24/rc>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board

of the Third Hospital of Shanxi Medical University (No. YXLL-2021-006) and informed consent was taken from all the patients.

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