Coronary stenosis is a risk marker for impaired cardiac function on cardiopulmonary exercise test

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Abstract

Background: Cardiac function varies in different ways in ischemic heart disease (IHD). We aimed to evaluate the characteristics of cardiac function on cardiopulmonary exercise test (CPET) in IHD with different coronary stenoses.

Methods: Totally 614 patients with IHD were divided into non-obstructive coronary artery disease (NOCAD) (stenosis < 50%), obstructive coronary artery disease (OCAD) (stenosis 50-90%) and severe OCAD (stenosis > 90%) according to the coronary angiography. And 101 healthy volunteers as controls. All participants performed CPET to assess cardiac function by oxygen uptake (VO2), estimated cardiac output (CO), and heart rate (HR).

Results: Generally, the values of VO2, CO, and HR in IHD were significantly lower than in healthy volunteers. Among 289 NOCAD, 132 OCAD, and 193 severe OCAD, significantly decreased values of VO2 peak: 16.01 ± 4.11 vs. 15.66 ± 4.14 vs. 13.33 ± 3.4 mL/min/kg; CO: 6.96 ± 2.34 vs. 6.87 ± 2.37 vs. 6.05 ± 1.79 L/min; HR: 126.44 ± 20.53 vs. 115.15 ± 18.78 vs. 109.07 ± 16.23 bpm, P < 0.05). NOCAD had significantly lower VO2 at anaerobic threshold (-1.35, 95%CI -2.16 - -0.54) and VO2 peak (-2.05, 95%CI -3.18 - -0.93) compared with healthy volunteers after adjustment. All IHD patients were associated with low stroke volume and inefficient gas exchange (P < 0.05).

Conclusion: IHD with increasing atherosclerotic burdens were associated with impaired cardiac output and chronotropic response on CPET. NOCAD should be given more early prevention and rigorous follow-up.

Keywords: Cardiac function, Cardiopulmonary exercise test, Ischemic heart disease, Atherosclerosis

Introduction

Ischemic heart disease (IHD) manifests in numerous ways, from non-obstructive coronary disease (NOCAD) to obstructive coronary disease (OCAD). Coronary atherosclerotic burden measured using invasive and non-invasive anatomic imaging modalities has been consistently demonstrated to be a powerful independent prognostic determinant of risk for heart failure (HF) and death [1–3]. The presence of cardiac dysfunction may be indicative of severe coronary stenosis, though no sufficient data demonstrated dose-response relationship [1]. Strategies based on the anatomical structure (e.g., coronary angiography (CAG), coronary computed tomographic angiography (CTA)) are useful for patients with OCAD, but not for patients with NOCAD that lacking of evident stenosis for large coronary vessels [4]. The methods of functional evaluation, instead, can assess IHD from the perspective of cardiac function regardless of the stenosis severity [4, 5].

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Cardiopulmonary exercise test (CPET) is a noninvasive and safe approach to assess cardiopulmonary function and helps understand underlying pathophysiological mechanisms [6]. CPET for IHD assessment is an area of growing clinical interests [7] since it provides a thorough assessment of exercise integrative physiology involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems [8]. Combination of cardiac electrophysiology variables (e.g., heart rate (HR) and electrocardiogram (ECG)) and gas exchange variables (e.g., oxygen uptake (VO2), O2 pulse (VO2/HR), VO2 relative to work-rate (VO2/WR)) [8–14] give clinicians unique insights on the evaluation of IHD [15–19]. The diagnostic and prognostic role of CPET in IHD have been confirmed in previous studies [7, 11, 13, 18, 20]. However, the difference of cardiac function on CPET in IHD with different coronary atherosclerotic burdens is unknown. The purpose of the study is to analyze cardiac functional characteristics of IHD on CPET with different coronary atherosclerotic burdens.

Methods
Study population
This was a cross-sectional observational study that included ischemic symptomatic patients in Beijing Tingshua Changgung Hospital from March 2018 to September 2019. The ischemic symptomatic patients that had either typical or atypical angina on Rose questionnaire [21] were divided into three groups according to the degree of coronary stenosis by CAG: (1) NOCAD: those that had ischemic symptoms but all the coronary arteries stenosis less 50%; (2) OCAD: those that had ischemic symptoms and had at least one of the coronary arteries stenosis from 50 to 90%; (3) severe OCAD: those that had ischemic symptoms and had at least one of the coronary arteries stenosis from 90 to 100%. Patients with a history of asthma, chronic obstructive pulmonary disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, and valvular heart disease were excluded. In addition, we enrolled 101 healthy volunteers as controls according to the following criteria: > 18 years old; no symptoms of chest discomfort; no reported history of cardiovascular disease or pulmonary disease; no contradictions for exercise until achieving a respiratory exchange ratio (RER) ≥ 1.10 or HR peak ≥ 85% predicted HR peak [22]. Peak values were expressed as the 30-second-average at the highest workload achieved [6]. Anaerobic threshold (AT) was defined as the moment where lactic acid production exceeded its removal, determined by the V slope method or, if unclear, by the ventilator equivalent method [6].

VO2, predicted% VO2 peak, VO2/WR slope, VO2/HR, estimated cardiac output (CO), RER, etc. were automatically calculated by the Blue Cherry Software. CO was calculated by dividing VO2 by the arterial-venous oxygen content difference ([IC(a-v)O2]), using the Fick principle. Predicted HR peak was calculated as (220 – age) on no β-blocker therapy and (119 + 0.5 × HR rest – 0.5 × age) on β-blocker therapy. HR/WR was calculated as HR divided by WR at AT or peak, respectively. We constructed exercise/rest ratio (peak/rest, AT/rest) for the below variables: HR, VO2, VO2/HR, CO.

Statistical analysis
Participants were compared between below groups: healthy volunteers, NOCAD, OCAD, severe OCAD. Continuous variables with normal distribution were reported as the mean ± SD and tested by one-way ANOVA while non-normal distribution reported as median and interquartile range (IQR) and tested by Wilcoxon rank-sum test. Categorical variables were reported as percentages. Among-group comparisons were made using a $\chi^2$ test or a Fisher’s exact test if any expected cell count was less than five. Histograms were plotted to describe the distribution of CPET variables in healthy volunteers. 98% and 2% percentile were considered to be the lower and upper limits in our sample population.

We first modeled each CPET variable as the continuous variable separately against the four groups using the general linear model. Model 1 was the univariate model. Model 2 additionally adjusted for age and gender. Model 3 additionally adjusted for body mass index (BMI), compared with model 2. Model 4 additionally adjusted for use of HR limiting medication (e.g. metoprolol, diltiazem) compared with model 3. BMI was omitted from models for VO2 since they were already adjusted for weight. Age, gender, BMI were omitted from models for predicted %
VO₂ since they were already adjusted. HR and HR exercise/rest ratio were additionally adjusted for WR since we assumed it as the confounder. Adjusted LS-means with 95% CI were plotted for each group. Tukey-Kramer was used for adjustment for p-value for multi-groups comparison. For categorical CPET variables, the Chi-square test was used for univariate analysis. The logistic regression model for binary outcomes and polytomous logistic regression model for multi-nominal variables, adjusted for the aforementioned confounders, were constructed for multivariate analysis.

Participants were categorized by cardiac function and pathophysiological patterns. Cardiac function evaluation was defined according to EACPR/AHA statement [9]. Pathophysiological patterns were defined according to AHA evaluation paradigm [22]. Briefly, chronotropic insufficiency was defined as high VO₂/HR and low peak HR; low stroke volume (SV) was defined as low VO₂ peak or low VO₂/WR slope or low VO₂/HR; inefficient pulmonary gas change was defined as high VE/VCO₂ or high Vd/Vt. Cut-off value for each variable was derived from reference value in our healthy participants.

We performed sensitivity analysis using the criteria below: (1) excluded participants with insufficient effort (i.e. RER < 1.10 or HR peak < 85% predicted HR peak); (2) excluded participants taking HR limiting medications; (3) adjusted for history of hypertension, diabetes and hyperlipidemia in addition to model 4.
Statistical analysis was carried out in SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

The study population comprised of 614 patients with a mean age of 60 years and 101 healthy volunteers with a mean age of 37 years (Fig. 1). Severe OCAD patients were more younger, and had a higher BMI and HbA1c and high sensitivity cardiac troponin T and NT-proBNP, and had a higher incidence of hyperlipidemia compared with NOCAD and OCAD patients. NOCAD patients had the highest percent of women and the highest levels of low density lipoprotein cholesterol. And severe OCAD patients had the largest left ventricular end-diastolic dimension (LVEDD) and the lowest left ventricular ejection fraction (LVEF) (Table 1). There were 341 (47.7%) achieved RER ≥ 1.1, 632 achieved HR peak ≥ 85% predicted HR peak, a total of 669 (93.6%) participants achieved RER > 1.1 or HR peak > 85% predicted HR peak.

Cardiac output in IHD

Generally, VO$_2$ and CO in IHD were significantly lower than in healthy volunteers (Table 2). With increasing atherosclerotic burdens, significantly decreasing values of VO$_2$, CO, VO$_2$/HR. Multivariate analysis showed that with increasing atherosclerotic burdens, the decreasing trends for VO$_2$ AT and VO$_2$ peak were observed ($P<0.05$). For pairwise comparison, we especially noticed a significant decrease of VO$_2$ AT (β for NOCAD where the healthy as the reference, -1.35; 95% CI -2.16 - -0.54), VO$_2$ peak (β for NOCAD where the healthy as the reference, -2.05; 95% CI -3.18 - -0.93) in NOCAD (Fig. 2A). And CO dropped dramatically in severe OCAD but only slightly declined in NOCAD (Fig. 2B). VO$_2$/HR declined in severe OCAD patients but no significant difference was observed between NOCAD and healthy volunteers (Fig. 2C).

Table 1. Baseline characteristics of study population

| Variables          | Healthy (N = 101) | NOCAD (N = 289) | OCAD (N = 132) | Severe OCAD (N = 193) | p-value |
|--------------------|-------------------|-----------------|----------------|-----------------------|---------|
| Age (year)         | 36.93 ± 12.15     | 60.11 ± 10.46   | 61.82 ± 10.45  | 57.14 ± 10.55         | < 0.0001|
| Female, N (%)      | 59 (58.42%)       | 161 (55.71%)    | 34 (26.37%)    | 42 (22.11%)           | < 0.0001|
| BMI (kg/m$^2$)     | 23.4 ± 3.33       | 25.49 ± 3.36    | 25.16 ± 3.65   | 25.66 ± 3.35          | < 0.0001|
| Hypertension, N (%)| 0 (0%)            | 178 (62.02%)    | 96 (72.73%)    | 112 (58.64%)          | < 0.0001|
| Hyperlipidemia, N (%)| 0 (0%)         | 181 (63.07%)    | 105 (79.55%)   | 167 (87.43%)          | < 0.0001|
| Diabetes, N (%)    | 0 (0%)            | 74 (25.78%)     | 54 (40.91%)    | 52 (27.3%)            | < 0.0001|
| β-blocker, N (%)   | 0 (0%)            | 56 (21.71%)     | 49 (40.83%)    | 116 (67.05%)          | < 0.0001|
| Diltiazem, N (%)   | 0 (%)             | 9 (3.48%)       | 6 (5.00%)      | 5 (2.19%)             | < 0.0001|
| Haemoglobin (g/l)  | 134.77 ± 17.62    | 139.32 ± 13.8   | 136.7 ± 15.87  | 138.95 ± 15.77        | 0.21    |
| hs-cTnT (ng/ml)    | 0.00 (0.01)       | 0.01 (0.01)     | 0.01 (0.01)    | 0.05 (0.01)           | < 0.0001|
| NT-proBNP (pg/dl)  | 89 (54.136)       | 57 (25.97)      | 93 (38.154)    | 269 (110.5.587)       | < 0.0001|
| Fasting glucose (mmol/l) | 5.62 ± 0.9 | 5.9 ± 1.65      | 6.06 ± 1.59    | 6.31 ± 2.01           | 0.04    |
| eGFR (ml/min*1.73m$^2$) | 107.46 ± 15.33 | 93.76 ± 14.31   | 88.29 ± 17.59  | 89.29 ± 16.51         | < 0.0001|
| TC (mmol/l)        | 4.59 ± 0.86       | 4.6 ± 0.94      | 3.75 ± 0.87    | 4.13 ± 0.99           | < 0.0001|
| TG (mmol/l)        | 1.52 (0.96,1.24)  | 1.42 (1.05,1.95)| 1.24 (0.88,1.8)| 1.61 (1.17,2.03)      | 0.25    |
| HDL-C (mmol/l)     | 1.16 ± 0.24       | 1.15 ± 0.29     | 1.05 ± 0.26    | 0.93 ± 0.21           | < 0.0001|
| LDL-C (mmol/l)     | 2.77 ± 0.87       | 2.81 ± 0.88     | 2.08 ± 0.66    | 2.58 ± 0.93           | < 0.0001|
| HbA1c (%)          | 5.73 ± 0.56       | 6.12 ± 1.02     | 6.25 ± 0.86    | 6.45 ± 1.52           | 0.02    |
| LVEDD (mm)         | 45.54 ± 3.37      | 46.65 ± 3.83    | 48.03 ± 4.07   | 49.33 ± 4.68          | < 0.0001|
| LVEDV (ml)         | 95.79 ± 16.89     | 101.59 ± 19.72  | 108.76 ± 21.25 | 116.04 ± 26.12        | < 0.0001|
| LVESD (mm)         | 26.75 ± 3.56      | 28.04 ± 3.42    | 29.63 ± 4.24   | 30.95 ± 5.11          | < 0.0001|
| LVEF (%)           | 65.57 ± 2.86      | 65.43 ± 3.43    | 63.88 ± 5.39   | 58.46 ± 8.82          | < 0.0001|

NOCAD Non-obstructive coronary artery disease, OCAD Obstructive coronary artery disease, severe OCAD severe obstructive coronary artery disease, BMI Body mass index, WBC White blood cell count, PLT Platelet, hs-cTnT High sensitivity cardiac troponin T, NT-proBNP N-Terminal pro-brain natriuretic peptide, eGFR Estimated glomerular filtration rate, TC Total cholesterol, TG Total triglycerides, HDL-C High density lipoprotein cholesterol, LDL-C Low density lipoprotein cholesterol, HbA1c Glycosylated hemoglobin, LVEDD Left ventricular end-diastolic dimension, LVEDV Left ventricular end-diastolic volume, LVESD Left ventricular end-systolic dimension, LVEF Left ventricular ejection fraction
Table 2  Univariate analysis for CPET variables

| Variables | Healthy (N = 101) | NOCAD (N = 289) | OCAD (N = 132) | Severe OCAD (N = 193) | p-value |
|-----------|------------------|-----------------|----------------|-----------------------|---------|
| **Resting value** | | | | | |  
| \( \text{VO}_2 \) rest (ml/min/kg) | 3.71 ± 0.78 | 3.1 ± 0.57 | 3.22 ± 0.57 | 3.21 ± 0.56 | < 0.0001 |
| CO rest (l/min) | 3.2 ± 1.36 | 2.73 ± 0.73 | 2.79 ± 0.68 | 2.76 ± 0.58 | < 0.0001 |
| HR rest (beats/min) | 79.77 ± 11.38 | 75.73 ± 10.79 | 72.84 ± 10.56 | 73.75 ± 10.15 | < 0.0001 |
| \( \text{VO}_2/\text{HR} \) rest (ml/beat) | 2.96 ± 0.89 | 2.85 ± 0.79 | 3.08 ± 0.77 | 3.13 ± 0.7 | 0.0006 |
| **AT value** | | | | | |  
| \( \text{VO}_2 \) AT (ml/min/kg) | 15.21 ± 4.42 | 11.79 ± 2.74 | 11.33 ± 2.55 | 10.41 ± 2.37 | < 0.0001 |
| CO AT (l/min) | 7.72 ± 2.89 | 6.15 ± 1.93 | 6.05 ± 1.86 | 5.51 ± 1.47 | < 0.0001 |
| HR AT (beats/min) | 123.24 ± 18.89 | 105.03 ± 14.18 | 97.53 ± 13.05 | 96.98 ± 11.86 | < 0.0001 |
| \( \text{VO}_2/\text{HR} \) AT (ml/beat) | 8.12 ± 2.33 | 7.9 ± 2.25 | 8.17 ± 2.17 | 7.95 ± 1.95 | 0.02 |
| \( \text{HR}/\text{WR} \) AT (beats/min/W) | 1.51 ± 0.42 | 1.65 ± 0.56 | 1.59 ± 0.47 | 1.82 ± 0.64 | < 0.0001 |
| WR AT (W) | 89.67 ± 34.38 | 69.62 ± 22.04 | 66.55 ± 20.43 | 58.14 ± 17.42 | < 0.0001 |
| **Peak Value** | | | | | |  
| \( \text{VO}_2 \) peak (ml/min/kg) | 21.61 ± 5.83 | 16.01 ± 4.11 | 15.66 ± 4.14 | 13.33 ± 3.4 | < 0.0001 |
| Predicted %\( \text{VO}_2 \) peak (%) | 66.96 ± 13.15 | 68.08 ± 15.09 | 62.02 ± 15.84 | 49.7 ± 13.23 | < 0.0001 |
| CO peak (l/min) | 8.85 ± 3.16 | 6.96 ± 2.34 | 6.87 ± 2.37 | 6.05 ± 1.79 | < 0.0001 |
| Predicted %CO peak (%) | 54.66 ± 10.68 | 51.19 ± 10.98 | 48.35 ± 12.2 | 40.18 ± 10.07 | < 0.0001 |
| HR peak (beats/min) | 149 ± 22.96 | 126.44 ± 20.53 | 115.15 ± 18.78 | 109.07 ± 16.23 | < 0.0001 |
| \( \text{VO}_2/\text{HR} \) peak (ml/beat) | 9.52 ± 2.72 | 8.95 ± 2.62 | 9.6 ± 2.7 | 9 ± 2.28 | 0.03 |
| \( \text{HR}/\text{WR} \) peak (beats/min/W) | 1.2 ± 0.34 | 1.37 ± 0.46 | 1.32 ± 0.49 | 1.51 ± 0.47 | < 0.0001 |
| WR peak (W) | 135.81 ± 46.49 | 102.55 ± 36.34 | 98.38 ± 36.91 | 79.19 ± 28.2 | < 0.0001 |
| VE/V\( \text{CO}_2 \) slope | 25.56 ± 3.95 | 28.89 ± 5.1 | 30.14 ± 5.65 | 29.68 ± 5.61 | < 0.0001 |

NOCAD Non-obstructive coronary artery disease, OCAD Obstructive coronary artery disease, severe OCAD severe obstructive coronary artery disease, \( \text{VO}_2 \): Oxygen input, CO Cardiac output, HR Heart rate, AT Anaerobic threshold, RER Respiratory exchange rate, WR Work rate
HR in IHD was significantly lower than in healthy volunteers (Table 2). With increasing atherosclerotic burdens, a significantly decreased value of HR was observed (Table 2). Multivariate analysis showed that HR was lower for OCAD compared with NOCAD (Fig. 3 A); a significant decrease of HR AT/rest was observed for NOCAD \( (P < 0.05) \) (Fig. 3B); an overall increasing pattern was noticed for HR/WR (AT and peak), which especially rocketed in severe OCAD patients (Fig. 3 C).

**Pathophysiological patterns in IHD**

Generally, compared with healthy volunteers, participants with IHD had much higher frequency of abnormal circulatory impairment pattern (Fig. 4). All IHD patients were overall associated with low SV and inefficient gas exchange \( (P < 0.05) \). For distinctive groups, only severe OCAD was associated with low SV associated with inefficient gas exchange (Table 3). No significant results were observed for OCAD or NOCAD in adjusted model.

**Discussion**

To our knowledge, this is the first study that comprehensively compared the characteristics of cardiac function on CPET among NOCAD, OCAD, and severe OCAD patients. In this study we found: (1) with increasing atherosclerotic burdens, patients had the impaired cardiac output \( (\text{VO}_2, \text{CO}) \) and chronotropic response \( (\text{HR}, \text{HR exercise/rest ratio}) \); (2) significant differences between NOCAD and healthy volunteers were noticed for \( \text{VO}_2 \) and HR AT/rest in pairwise comparison after adjustment for confounders; (3) IHD patients were overall associated with low SV and inefficient gas exchange, especially severe OCAD. CPET is a useful tool to evaluate the cardiac function in different atherosclerotic burdened IHD that should be implied in the clinic to guide the management and treatment of IHD. Especially, for NOCAD patients, even if there is no further microcirculation anatomical evidence, cardiac functional evaluation by CPET can be used...
to stratify the cardiac risk. For NOCAD patients with abnormal functions, early prevention and rigorous follow-up are important measures to decrease the adverse cardiac events.

Cardiac function is manifested in cardiac output and chronotropic response. Some key variables were used as surrogates for cardiac output per minute, stroke volume as well as a direct measure of HR response [7]. In patients with cardiac dysfunction, myocardial oxygen deficit during exertion-induced mechanical dysfunction exceed the ischemic threshold, resulting in stroke volume to decrease with the progressively increasing workload. Therefore, the sympathetic activity up-regulated to accelerate HR as a compensation mechanism. The abrupt plateau or decrease in stroke volume was accompanied by a decrease in cardiac output, reflected by VO2 [9–13]. A more blunted VO2 response was consistent with cardiac severe status [7]. In this study, we compared the difference of the cardiac function by CPET in IHD patients with different atherosclerotic burdens (NOCAD, OCAD, severe OCAD). In our IHD patients, the performance on cardiac output (VO2, CO, VO2/HR) and chronotropic response (HR) on CPET worsened with increasing atherosclerotic burdens (severe OCAD worst, OCAD moderate, NOCAD best). Because of atherosclerotic burden, the exercise induced ischemia leaded to the acute decrease of cardiac output on CPET in our IHD patients.

Few studies focused on cardiac function assessed by CPET in different coronary atherosclerotic burdened IHD. Akinci Ozyurek et al [23] selected subjects with chest pain to undergo CPET and CAG, and found that peak VO2 and VO2/HR were higher in patients with normal angiographic results than those with OCAD, though without statistical significance; HR peak was higher in subjects with OCAD than in subjects without OCAD. Hassan Khan et al [24] reported that peak VO2 was significantly lower in OCAD than in participants without OCAD (28.3±8.1 VS 31.2±7.7 ml/kg/min, P<0.01) in the Kuopio Ischemic Heart Disease Risk Factor Study. Ellen Coeckelberghs et al [18] reported that 1409 IHD patients composed of AMI and OCAD had peak VO2 19.5±5.6 ml/kg/min and 73±17% of predicted and peak HR 124±21 bpm. Bong-Joon Kim et al [25] concentrated on the elderly patients with cardiovascular disease in Korea that showed an average exercise capacity of 21.3±5.5 ml/kg/min at peak VO2, and men showed better exercise capacity than women on most CEPT parameters. Compared with previous studies, [18, 23–25] our IHD patients in different coronary atherosclerotic burdens generally had a lower levels of VO2 peak (16.01±4.92 ml/kg/min), predicted% VO2 peak (61.84±16.38%), VO2/HR (9.17±2.57 ml/beat) that may be partially attributed to racial differences.

VO2 peak, recognized as cardiorespiratory fitness, [15] was proposed as a vital indicator of prognosis in IHD [26]. Declined VO2 peak was related to lower levels of aerobic capacity and could indicate subclinical pathophysiology [16]. Increased VO2 peak could have substantial benefits in reducing the burden of IHD [27]. Chaudhry [28] illustrated a considerable decline in VO2 peak and VO2/HR in male NOCAD and a slight decrease in female NOCAD. VO2 peak and VO2 AT were significantly attenuated in cardiac syndrome X, [29] and women with NOCAD had markedly reduced VO2 peak [20]. In our study, VO2 at AT and peak decreased with increasing atherosclerotic burdens that suggested a deterioration of cardiac function in our IHD patients. In accord with previous studies, our NOCAD patients had a lower VO2 than healthy participants that may related to the microcirculation dysfunction should be emphasized to trace the cardiovascular risk factors to early prevent and follow up.

Chaudhry [28] observed a pathological HR response in NOCAD and abnormal HR response was more effective than stress ECG test for identifying cardiac dysfunction. HR/WR slope reclassified abnormalities in the NOCAD from 22 to 81%. In our study, a significant difference of HR/WR between NOCAD and healthy participants was not detected after adjustment. HR/WR was defined as the value at a specific time (AT, peak) in our study, which was not exactly the change in HR as a function of WR in the last 2 min of exercise as Chaudhry’s study. Particularly, the greater decline of WR relative to HR in NOCAD might lead to a slightly increased ratio of HR/WR, which implied an impaired exercise capacity. More study should focus on the impact of WR on performance of CPET and the complex role of other compounds factors in CPET.

NOCAD was a marker of the more adverse risk factor profile [30]. CPET was also used to expand the
Fig. 3 (See legend on previous page.)
role in microvascular coronary heart disease, beyond identifying flow-limiting lesions [31]. Subjects with either macrovascular or microvascular coronary heart disease could demonstrate a similar CPET response, although cardiac catheterization findings may be different [31]. Thus, we applied CPET to evaluate the NOCAD patients in our study. It was noticeable that compared with healthy volunteers, some NOCAD patients performed worse even after adjustment, namely, lower VO\textsubscript{2} peak, and HR response. More studies demonstrated that abnormal dilatory responses of the coronary microvessels and coronary microvascular spasm were identified as pathogenic mechanisms in both chronic and acute forms of ischemic heart disease [5, 32]. It was supposed that the microcirculation dysfunction was related to the decrease of coronary

**Table 3** Odds ratio for potential pathophysiological patterns

|                  | NOCAD                  |            | OCAD                  |            | Severe OCAD       |            |
|------------------|------------------------|------------|----------------------|------------|-------------------|------------|
|                  | Model                  | OR (95%CI) | p*                   | OR (95%CI) | p*                | OR (95%CI) | p*         |
|                  |                        |            |                      |            |                   |            |
| Low stroke volume| 1                      | 3.92 (1.52, 10.14) | 0.0048               | 2.91 (1.04, 8.19) | 0.0426          | 6.86 (2.64, 17.82) | < 0.0001  |
|                  | 2                      | 1.76 (0.61, 5.04) | 0.2952               | 1.53 (0.48, 5.01) | 0.477            | 4.73 (1.63, 13.68) | 0.0042    |
|                  | 3                      | 1.81 (0.62, 5.26) | 0.2751               | 1.57 (0.48, 5.08) | 0.4537          | 4.87 (1.66, 14.26) | 0.0039    |
|                  | 4                      | 2.77 (0.75, 10.24) | 0.1273               | 2.61 (0.64, 10.61) | 0.1802          | 6.81 (1.78, 26.08) | 0.0051    |
| Inefficient gas exchange | 1 | 5.79 (2.26, 14.82) | 0.0002               | 15.2 (5.83, 8.32) | < 0.0001        | 12.52 (4.87, 30.2) | < 0.0001  |
|                  | 2                      | 1.04 (0.37, 2.95) | 0.9384               | 1.93 (0.65, 5.69) | 0.2336          | 2.21 (0.78, 6.22) | 0.1337    |
|                  | 3                      | 1.33 (0.47, 3.82) | 0.5928               | 2.40 (0.87, 7.21) | 0.1186          | 2.82 (0.99, 8.04) | 0.0525    |
|                  | 4                      | 1.33 (0.41, 4.28) | 0.6367               | 2.21 (0.65, 7.49) | 0.2024          | 2.96 (0.91, 9.67) | 0.0728    |

*Healthy participants as reference group. Model 1 was univariate model. Model 2 additionally adjusted for age and gender. Model 3 additionally adjusted for BMI, compared with model 2. Model 4 additionally adjusted for use of HR limiting medications.
oxygen uptake and cardiac output that manifesting as lower VO₂ and CO in NOCAD compared to the healthy participants. We extrapolated those NOCAD patients to have impaired cardiac function and poor prognosis. Though invasive microvascular function tests were not conducted, CPET variables still conveyed substantial information for evaluation of the function and prognosis in NOCAD. And the demonstration of coronary microvascular dysfunction in NOCAD (i.e., reduced coronary flow reserve or microvascular spasm) can be investigated during angiography using intracoronary adenosine and ACh.

Our study has several limitations: (1) This is a single-center study that may introduce selection bias. (2) Healthy participants were younger than symptomatic patients. We were not able to enroll enough age and gender-matched symptomatic and healthy participants. But we adjusted for age in the study and help to reduce the impact of confounding.

**Conclusion**

Associations were observed between increasing atherosclerotic burdens and unfavorable CPET variables for cardiac output and chronotropic response. NOCAD patients had a lower VO₂ peak and HR response compared with healthy volunteers that should be given more early prevention and rigorous follow-up. CPET can be a useful tool to evaluate cardiac function in different atherosclerotic burdened heart diseases.

**Abbreviations**

BMI: Body mass index; CAG: Coronary angiography; [C(a-v)O2]: Arterial-venous oxygen content difference; CO: Estimated cardiac output; CPET: Cardiopulmonary exercise test; CTA: Coronary computed tomographic angiography; ECG: Electrocardiogram; HR: Heart rate; IHD: Ischemic heart disease; LVEDD: Left ventricular end-diastolic dimension; LVEF: Left ventricular ejection fraction; NOCAD: Non-obstructive coronary artery disease; OCAD: Obstructive coronary artery disease; SV: Stroke volume; VO₂: Oxygen uptake.

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**Authors’ contributions**

Ping Zhang contributed to conception and interpretation; Siyuan Li, Yifang Yuan, and Lanting Zhao contributed to conception and design and draft manuscript and acquisition analysis; Yifang Yuan contributed to design and analyze data; Lanting Zhao and Siyuan Li contributed to perform experiments and interpretation; Tingting Lv and Yu Geng critically revised the manuscript and interpretation; Fei She, Fang Liu, Yajun Xue, Boda Zhou, Ying Xie contributed to perform experiments. All authors reviewed the manuscript.

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**Availability of data and materials**

The datasets generated and analyzed during the current study are not publicly available due privacy and ethical restrictions but are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by ethics board of Beijing Tsinghua Changgung Hospital and informed consent was taken from all individual participants.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

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