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The association between O_2-pulse slope ratio and functional severity of coronary stenosis: A combined cardiopulmonary exercise testing and quantitative flow ratio study

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ABSTRACT

Background: The role of cardiopulmonary exercise testing (CPET) parameters in evaluating the functional severity of coronary disease remains unclear. The aim of this study was to quantify the O_2-pulse morphology and investigate its relevance in predicting the functional severity of coronary stenosis, using Murray law-based quantitative flow ratio (μQFR) as the reference.

Methods: CPET and μQFR were analyzed in 138 patients with stable coronary artery disease (CAD). The O_2-pulse morphology was quantified through calculating the O_2-pulse slope ratio. The presence of O_2-pulse plateau was defined according to the best cutoff value of O_2-pulse slope ratio for predicting μQFR $\leq$ 0.8.

Results: The optimal cutoff value of O_2-pulse slope ratio for predicting μQFR $\leq$ 0.8 was 0.4, with area under the curve (AUC) of 0.632 (95 % CI: 0.505–0.759, $p = 0.032$). The total discordance rate between O_2-pulse slope ratio and μQFR was 27.5 %, with 13 patients (9.4 %) being classified as mismatch (O_2-pulse slope ratio $>$ 0.4 and μQFR $\leq$ 0.8) and 25 patients being classified as reverse-mismatch (O_2-pulse slope ratio $\leq$ 0.4 and μQFR $>$ 0.8). Angiography-derived microvascular resistance was independently associated with mismatch (OR 0.07; 95 % CI: 0.01–0.38, $p = 0.002$) and reverse-mismatch (OR 9.76; 95 % CI: 1.47–64.82, $p = 0.018$).

Conclusion: Our findings demonstrate the potential of the CPET-derived O_2-pulse slope ratio for assessing myocardial ischemia in stable CAD patients.

1. Introduction

Coronary artery disease (CAD) remains the most prevalent health concern globally, upholding its position as the leading cause of morbidity and mortality[1]. The early diagnosis of CAD is essential for the proper management of patients. Although coronary angiography is widely considered the gold standard for diagnosing CAD, its invasive nature, high cost, and limited availability in primary care settings preclude it from being a first-line diagnostic tool, except in cases where patients have a high likelihood of obstructive CAD[2]. On the other hand, the exercise electrocardiogram (ECG) is a simple and cost-effective test that can serve as a clinically relevant screening method to justify the appropriateness of invasive procedures. However, recent randomized clinical trials have raised concerns regarding its diagnostic performance compared to other imaging diagnostic tests [3–6].

Cardiopulmonary exercise testing (CPET), a combination of exercise stress testing with ventilatory gas exchange measurements, has increasingly gained recognition for its utility in diagnosing the causes of unexplained dyspnea[7], comprehensively assessing cardiac functions [8–10], and predicting the prognosis of patients with heart disease [11,12]. More recently, CPET has gradually emerged as a widely used non-invasive evaluation method for myocardial ischemia in clinical practice. Compared to the traditional ECG stress test, CPET has demonstrated superior sensitivity and specificity in detecting inducible myocardial ischemia and perfusion defects[13–15].

The O_2-pulse, derived from CPET, stands as one of the most valuable

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indicators of myocardial ischemia[16–19]. It represents the ratio of oxygen consumption (VO_2) to heart rate (HR), effectively reflecting increments in stroke volume and oxygen extraction[20,21]. In particular, the flattening of the O_2-pulse curve serves as a surrogate for the decreased stroke volume that ensues from cardiac dysfunction triggered by ischemia during exercise[22]. Nevertheless, the assessment of O_2-pulse morphology primarily relies on subjective visual judgment, lacking a standardized and quantifiable criterion for evaluation. Furthermore, there remains a scarcity of data exploring the correlation between O_2-pulse morphology and other emerging indicators of coronary stenosis functionality, such as the Murray law-based quantitative flow ratio (μQFR)[23].

Therefore, the primary objective of this study is to quantify the O_2-pulse morphology and examine its concordance and discordance with μQFR.

2. Methods

2.1. Study design and patient population

This is a retrospective observational cross-sectional study that was conducted in Shanghai East Hospital (Tongji University School of Medicine). Consecutive patients who exhibited symptoms indicative of stable coronary artery disease (CAD) and referred to Shanghai East Hospital (Tongji University School of Medicine) from July 2020 to December 2021 who submitted to CPET before angiography underwent initial screening. Exclusion criteria included all contraindications of CPET and coronary angiography, heart failure, other heart diseases (including congenital heart disease, valve disease, cardiomyopathy, etc.), lung diseases (including pulmonary hypertension, chronic obstructive pulmonary disease, interstitial lung disease, etc.), arrhythmia disorders (including atrial fibrillation, etc.), anemia, peripheral vascular diseases, muscle-related disorders. A sample size of 116 subjects would provide approximately 80 % power to detect a difference in CPET parameter equal to 0.47 on the basis of a Student's *t*-test with two-sided $\alpha = 0.05$[24].

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional ethics board of Shanghai East Hospital (No. 2022_286). The committee waived the need for informed consent due to the retrospective nature of the research.

2.2. Cardiopulmonary exercise testing

Before the coronary angiography procedure, a symptom-limited, physician-supervised CPET was conducted using an electromagnetically braked cycle ergometer with a breath-by-breath analysis of ventilation and exhaled gas. All tests adhered to the guidelines for CPET outlined by the the ATS/ACCP[25]. The exercise test comprised four phases, comprising a 3-minute baseline period, a 3-minute warm-up period, followed by the incremental exercise test, and finally, a 5-minute cool-down period post-exercise. Patients were instructed to maintain a constant pedaling rate of 60 ± 5 rpm throughout the test. Continuous monitoring including electrocardiographic, blood pressure, and oxygen saturation was conducted, and the respiratory gases was collected through the mask. The test continued until the patient reached their maximum exercise capacity or exhibited signs of fatigue defined as rating of perceived exertion between 15 and 16 on the Borgscale.

The following CPET parameters were recorded or further calculated according to the ATS/ACCP Statement recommendations: oxygen uptake (VO_2, mL/min), carbon dioxide output (VCO_2, mL/min), minute ventilation (VE, L/min), respiratory exchange ratio (RER), VO_2/work rate relationship ($\Delta VO_2/\Delta WR$, mL/min/W), O_2-pulse (VO_2/HR, mL/beat), VE/VCO_2, and breath reserve (BR, %). The anaerobic threshold (AT) was determined using the V-slope method. Peak values were defined as the average value of the last 15 s of exercise.

2.3. O_2-pulse slope ratio calculation

To quantitatively assess the trajectory of the O_2-pulse curve, we segmented it into early and late stages. We then calculated the slope changes within these two stages, as described in previous studies [26,27]. As shown in Fig. 1, we termed these slope changes the "O_2-pulse slope ratio". This ratio was derived by comparing the slope of the O_2-pulse curve during the final 2 min of exercise (designated as the late slope) with the slope during the remainder of the exercise duration until the final 2 min (designated as the early slope). The slope value of each stage was determined through linear regression analysis using the GraphPad prism 9.3.1 (GraphPad Software, Inc, La Jolla, CA, USA).

2.4. Murray law-based quantitative flow ratio measurement

μQFR was determined by an off-line calculation using a Murray law-based method (AngioPlus, Pulse Medical Imaging Technology, Shanghai Co., Ltd., Shanghai, China), as previously described[23]. Briefly, the operator identified the most promising angiographic projection and frame for optimal contouring of lumen coronary stenosis. The lumen contour of the main vessel and side branches exceeding 1 mm was delineated and the resting flow velocity (RFV) was automatically calculated. Subsequently, μQFR was calculated, based on the single projection, according to Murray's fractal low (illustrated in **Supplementary** Fig. 2).

From the aforementioned μQFR calculation process, various vessel characteristics such as minimum lumen diameter (MLD), diameters stenosis (DS), area stenosis (AS), lesion length, reference vessel diameter (RVD), were obtained. Additionally, the angiography-derived microvascular resistance (AMR) was automatically calculated as Pa*μQFR divided by the modeled hyperemic flow velocity according to the previously described methods[28]. In cases of multi-vessel disease, vessels with visually estimated diameter stenosis exceeding 30 % were evaluated, and the vessel with the lowest μQFR value was chosen for per-patient analysis.

2.5. Definitions of functional significance and mismatch

In the present study, a μQFR value of ≤ 0.8 was considered functionally significant. The optimal cutoff for O_2-pulse slope ratio in predicting the μQFR ≤ 0.8 was identified as indicating the presence of plateau. A mismatch was defined as follows: when the O_2-pulse slope ratio suggested a non-plateau, but the μQFR was ≤ 0.8. Conversely, a reverse-mismatch was characterized by the O_2-pulse slope ratio indicating a plateau despite the μQFR being > 0.8. Concordance, whether positive or negative, was determined when both O_2-pulse slope ratio and μQFR indicated positivity or negativity, respectively.

2.6. Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA), OriginPro Version2021 (OriginLab Corporation, Northampton, MA, USA) and R version 4.0.4. (R foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation (SD) and compared using the Student's *t*-test for intergroup comparisons. Categorical data were expressed as percentages and were analyzed using the Chi-square test. Receiver operating characteristic (ROC) curve was employed to determine the optimal cutoff value of O_2-pulse slope ratio for predicting the μQFR ≤ 0.8 applying Youden's index[29,30]. Linear regression was utilized to assess the relationships between continuous parameters. Multivariable logistic regression analysis was conducted to identify the independent predictors of discordance between oxygen pules plateau and μQFR-defined functional significance. Variables with a significance level $p < 0.1$ in univariable analysis and those considered clinically relevant were included in the final multivariable model, utilizing the

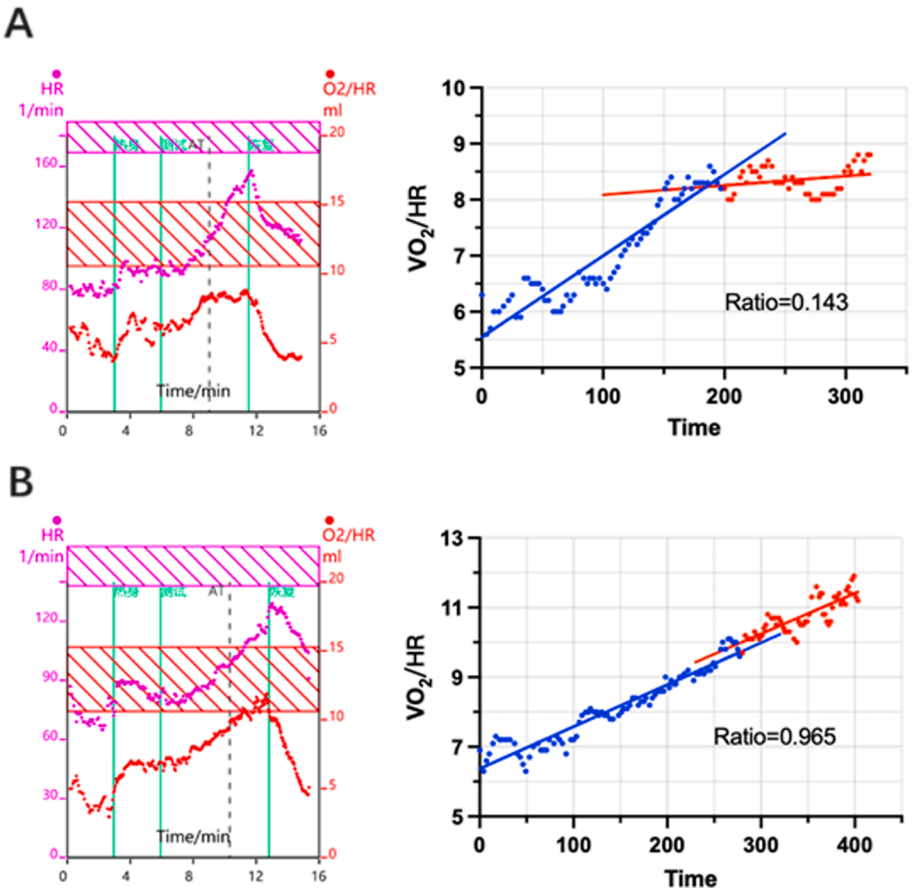

Fig. 1. Representative illustrations of O_2-pulse slope ratio calculation. A: Patient exhibiting a plateau; B: Patient exhibiting a non-plateau.

backward stepwise regression method. A two-sided p value < 0.05 was considered statistically significant for all analyses conducted in this study.

3. Results

3.1. Patient characteristics

Supplementary Fig. 1 shows the flowchart of patient enrollment. In this study, 295 patients underwent initial screening. Among them, 23 patients were excluded due to comorbidities. Additionally, 16 patients were excluded due to incomplete data during testing, an inability to complete CPET or deferral of coronary angiography. During the μQFR analysis process, 111 patients without stenosis exceeding 30 % and 2 patients with chronic total occlusion were excluded. Furthermore, 5 patients were excluded for the overlapping and suboptimal imaging quality. Consequently, a total of 138 patients were included in the final analysis. No myocardial infarction or death were observed because of the conducted tests. Among the 138 included patients, 28 patients exhibited μQFR $\leq$ 0.8, while 110 patients had μQFR $>$ 0.8. A detailed overview of patient clinical characteristics is provided in Supplementary Table 1. Significantly, the group with μQFR $\leq$ 0.8 demonstrated a higher prevalence of diabetes (46.4 % vs. 23.6 %, $p = 0.017$), multi-vessel disease (71.4 % vs. 29.1 %, $p < 0.001$), and a higher rate of ad hoc percutaneous coronary intervention (PCI) (35.7 % vs. 2.7 %, $p < 0.001$) compared to the μQFR $>$ 0.8 group.

3.2. Vessel characteristics

Final analysis encompassed 53 vessels in the μQFR $\leq$ 0.8 group and 148 vessels in the μQFR $>$ 0.8 group. Per-patient analysis, as shown in Supplementary Table 1, revealed several significant distinctions: lesions deemed functionally significant were longer (26.7 $\pm$ 10.9 mm vs. 18.5 $\pm$ 10.8 mm, $p = 0.001$) with higher diameter stenosis (49.9 $\pm$ 10.9 % vs. 34.0 $\pm$ 7.8 %, $p < 0.001$), more severe area stenosis (73.4 $\pm$ 10.7 % vs. 55.8 $\pm$ 10.5 %, $p < 0.001$) and smaller MLD (1.5 $\pm$ 0.5 mm vs. 2.0 $\pm$ 0.5 mm, $p < 0.001$). Moreover, the μQFR $\leq$ 0.8 group exhibited higher RFV (17.2 $\pm$ 5.4 m/s vs. 13.9 $\pm$ 4.8 m/s, $p = 0.002$) and lower AMR (1.6 $\pm$ 0.5 mmHg*s/cm vs. 2.7 $\pm$ 0.7 mmHg*s/cm, $p < 0.001$) compared to vessels in the μQFR $>$ 0.8 group.

3.3. CPET parameters

Table 1 presents the CPET parameters for patients categorized by μQFR values. In terms of traditional parameters associated with myocardial ischemia, no significant differences were observed in peak VO_2/kg, peak VO_2/HR, peak $\Delta VO_2/\Delta WR$ and ST segment changes. Patients within the μQFR $\leq$ 0.8 group showed a trend towards lower peak VO_2/kg of predicted value; however, this difference was not statistically significant compared to those in the μQFR $>$ 0.8 group (70.14 $\pm$ 12.72 % vs. 75.27 $\pm$ 14.32 %, $p = 0.086$). Notably, patients in the μQFR $\leq$ 0.8 group demonstrated a higher heart rate reserve (HRR) compared to those in the μQFR $>$ 0.8 group (40 $\pm$ 12 beats/min vs. 34 $\pm$ 16 beats/min, $p = 0.047$). Moreover, the O_2-pulse slope ratio was significantly lower in the μQFR $\leq$ 0.8 group compared to the μQFR $>$ 0.8 group (0.46 $\pm$ 0.90 vs. 0.93 $\pm$ 0.94, $p = 0.019$).

3.4. Association between O_2-pulse slope ratio and μQFR

ROC analysis demonstrated that the optimal cutoff value of O_2-pulse slope ratio for predicting μQFR $\leq$ 0.8 was 0.4 (AUC = 0.632, 95 % CI: 0.505–0.759, $p = 0.032$) (Fig. 2**A**). Utilizing this threshold, an O_2-pulse

Table 1
CPET characteristics stratified by the μQFR-defined functional severity.

	μQFR ≤ 0.8 (n = 28)	μQFR > 0.8 (n = 110)	P value
Exercise Time, s	427 ± 80	417 ± 108	0.654
Peak workload, W	101 ± 29	90 ± 29	0.081
Peak HR, beats/min	121 ± 16	124 ± 16	0.432
HRR, beats/min	40 ± 12	34 ± 16	0.047
Peak SBP, mmHg	161 ± 20	163 ± 24	0.807
Peak VO_2/kg, mL/kg/min	18.77 ± 3.57	18.9 ± 3.74	0.869
Peak VO_2/kg, % of predicted	70.14 ± 12.72	75.27 ± 14.32	0.086
$\Delta VO_2/\Delta WR$, mL/min/W	9.92 ± 1.45	10.4 ± 1.41	0.115
Peak VO_2/HR, mL/beat	11.04 ± 2.1	10.32 ± 2.61	0.179
Peak VO_2/HR, % of predicted	93.88 ± 18.97	98.12 ± 17.55	0.264
Peak VE, L/min	49.71 ± 14.23	44.55 ± 12.87	0.066
BR, %	50.28 ± 13.55	51.48 ± 12.57	0.658
VE/VCO_2 slope	29.65 ± 3.46	29.77 ± 4.84	0.906
ST-segment changes, n (%)	8(28.5)	16(14.5)	0.096
O_2-pulse slope ratio	0.46 ± 0.90	0.93 ± 0.94	0.019

Values are mean ± SD or number(percentage). BR = breath reserve; CPET = cardiopulmonary exercise testing; HR = heart rate; HRR = heart rate reserve; SBP = systolic blood pressure; μQFR = Murray law-based quantitative flow ratio; VE = ventilation; VCO_2 = carbon dioxide output; VO_2 = oxygen uptake; WR = work rate.

plateau was detected in 40 patients (29.0 %). Importantly, patients exhibiting an O_2-pulse plateau demonstrated significantly lower μQFR values compared to those without the plateau (0.81 ± 0.16 vs 0.89 ± 0.10, $p = 0.013$) (Fig. 2**B**). When analyzed as continuous variables, there was a suggestive positive correlation between the O_2-pulse slope ratio and μQFR ($p = 0.090$) (Fig. 2**C**).

3.5. Discordance between O_2-pulse slope ratio and μQFR

The overall discordance rate between the O_2-pulse slope ratio and μQFR was 27.5 %. Among these, mismatch (O_2-pulse slope ratio > 0.4 and μQFR ≤ 0.8) accounted for 9.4 % (13 patients), while reverse-mismatch (O_2-pulse slope ratio ≤ 0.4 and μQFR > 0.8) constituted 18.1 % (25 patients) (Fig. 3). In the multivariable analysis, higher BMI (OR 1.51; 95 % CI:1.12–2.03, $p = 0.007$), smoking status (OR 0.12; 95 % CI: 0.02–0.88, $p = 0.037$), higher RFV (OR 1.19; 95 % CI: 1.02–1.40, $p = 0.031$), lower AMR (OR 0.07; 95 % CI: 0.01–0.38, $p = 0.002$), and lower peak VO_2/kg of predicted value (OR 0.43; 95 % CI: 0.21–0.88, $p = 0.020$) were identified as independent predictors of mismatch. Conversely, higher RFV (OR 1.37; 95 % CI: 1.06–1.78, $p = 0.018$), higher AMR (OR 9.76; 95 % CI: 1.47–64.82, $p = 0.018$), higher peak HR (OR 1.03; 95 % CI: 1.00–1.07, $p = 0.048$) and lower peak $\Delta VO_2/\Delta WR$ (OR 0.61; 95 % CI: 0.40–0.93, $p = 0.020$) were identified as independent predictors of reverse-mismatch. Diabetes also showed a borderline-significant association with reverse-mismatch (OR 3.06; 95 % CI: 0.97–9.62, $p = 0.056$).

4. Discussion

The present study aimed to characterize the diagnostic features of a novel CPET-derived metric, O_2-pulse slope ratio, in predicting the functional severity of CAD. Our findings revealed that an O_2-pulse slope ratio of 0.4 was a predictor of μQFR-defined functional significance in assessing individuals with moderate to severe coronary stenosis.

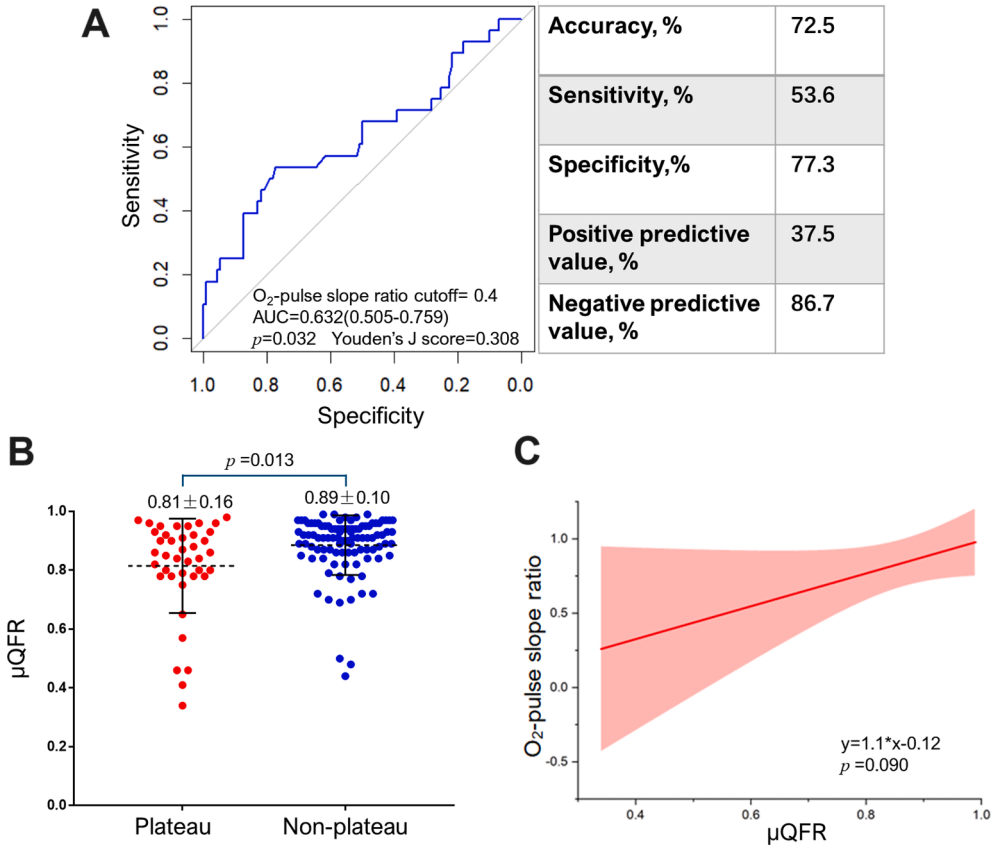

Fig. 2. Association between O_2-pulse slope ratio and μQFR. A: The ROC curve analysis and diagnostic performance of O_2-pulse slope ratio for predicting the μQFR ≤ 0.8. B: The comparison of μQFR stratified by the cutoff of O_2-pulse slope ratio. Dots represent all individual data points. Bars represent the mean and SD. **C:** Relationship between the O_2-pulse slope ratio and μQFR. The shaded area represents the 95 % CI of the linear regression equation. The AUC = area under the curve; μQFR = Murray law-based quantitative flow ratio; ROC = Receiver operating characteristic curve.

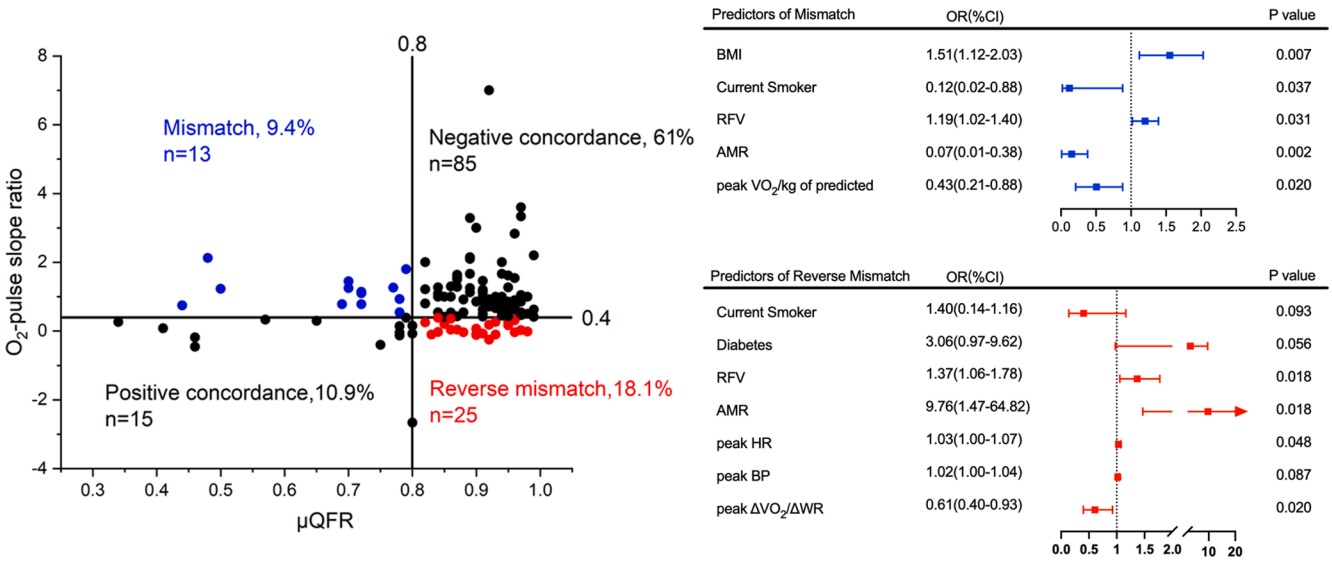

Fig. 3. Discordance between O_2-pulse slope ratio and μQFR and independent predictors of mismatch and reverse mismatch between these two functional indices. AMR = angiography-derived microvascular resistance; BMI = body mass index; RFV = resting flow velocity; μQFR = Murray law-based quantitative flow ratio.

However, a 27.5 % discrepancy rate between the two functional modalities was noted, potentially attributed to factors such as microcirculatory function and reduced exercise effort.

4.1. CPET-derived ischemia indicators

In exercise-induced ischemia, left ventricular dysfunction typically precedes the onset of symptoms and other manifestations, including electrocardiographic alterations[31]. Alterations in the oxygen pulse can predict the myocardial ischemia through providing an early estimate of left ventricular stroke volume changes during exercise[32]. Our findings further support this theory, revealing that the oxygen pulse metric, rather than ST-changes, is associated with the functional severity of ischemia. However, in the present study, other traditional ischemia indicators derived from CPET, such as peak VO_2/kg, peak VO_2/HR, and peak $\Delta VO_2/\Delta WR$, were not associated with the functional severity of coronary stenosis. This contrasts with previously reported studies but aligns with the findings of the ORBITAL trial[26]. This discrepancies in these results may be partially attributed to the diverse functional assessments employed across different studies[33,34].

4.2. Association between O_2-pulse slope ratio and μQFR

Our study highlighted a correlation between the O_2-pulse slope ratio and the functional severity of coronary stenosis expressed by μQFR. Notably, the optimal cutoff value for predicting μQFR $\leq$ 0.8 was 0.4, which aligns with the threshold utilized in the ORBITA trial for defining the presence of an O_2-pulse plateau[26]. This further emphasizes the diagnostic value of this novel morphological metric in assessing both the O_2-pulse plateau and functional severity of coronary stenosis. Previous studies examining O_2-pulse morphology's diagnostic capacity for ischemia yielded conflicting results[35–37], possibly due to the subjective or semi-quantitative nature of their definitions for the O_2-pulse plateau. Recently, Petek et al. investigated the diagnostic value of O_2-pulse plateau for obstructive CAD using a morphological metric that characterized the ratio of changes in O_2-pulse slope[27]. Despite similarities with our study, their quantitative O_2-pulse metric failed to predict obstructive CAD. However, their findings should be interpreted with caution due to the heterogeneous definition of obstructive CAD (using both CTA and angiography, and partial usage of wire-based physiological indices), the combined use of treadmill and cycle ergometer, and the above average fitness of their study population.

4.3. Discordance between O_2-pulse slope ratio and μQFR

To the best of our knowledge, the current study marks the inaugural investigation exploring the discordance between the O_2-pulse morphological metric and the coronary functional index in stable CAD patients. CPET serves as a comprehensive functional assessment, encompassing both macrovasculature and microcirculation, whereas QFR is regarded as a pure epicardial functional index [38–41]. In the current study, additional CPET-derived ischemia indicators such as peak HR and $\Delta VO_2/\Delta WR$ were indicators of reverse mismatch[16,22,42]. The alignment of these ischemia indicators suggests that CPET may detect the ischemia that lies beyond the scope captured by μQFR. Moreover, AMR, a virtual index of microvascular resistance, demonstrated independent associations with both mismatch and reverse-mismatch. Additionally, risk factors linked to microcirculatory dysfunction, like smoking and diabetes, might further exacerbate the flattening of O_2-pulse curve, resulting in a higher estimated functional severity from CPET. Collectively, these observations imply the significant role of microcirculatory dysfunction in the classification discrepancy between these two functional modalities, necessitating further investigation. Furthermore, our study emphasizes the importance of considering individual factors such as exercise capacity and body weight when interpreting O_2-pulse metrics in the assessment of myocardial ischemia among patients with stable CAD. Specifically, a lower peak VO_2/kg of predicted value and a higher BMI were found to be associated with mismatch. The higher body weight in patients often translates to lower exercise capacity, which can impact exercise effort and subsequently reduce the diagnostic sensitivity of the O_2-pulse metric in detecting flow-limiting CAD.

4.4. Potential clinical implication

Despite being recommended for obstructive CAD evaluation, CPET remains underused in routine clinical practice[22,25]. Several reasons contribute to this gap: CPET findings requiring specialized interpretation, the subjective nature of initial O_2-pulse morphology application lacking a clear threshold, and the necessity to exclude other conditions, such as non-ischemic heart failure or chronic lung disease.

Hence, our findings highlight the utility of the O_2-pulse slope ratio, offering a quantitative measure of O_2-pulse morphology, as an effective and practically applicable tool for myocardial ischemia detection. Notably, a slope ratio above 0.4 exhibited a high negative predictive

value (86.7 %), suggesting that CPET's potential as a gatekeeper for invasive procedures in stable CAD patients. Additionally, our findings provide novel insights into the potential use of CPET to assess the microcirculatory status, particularly in CPET-positive but μQFR-negative patients, which needs to be evaluated in future studies.

5. Limitation

This study has several limitations that need to be carefully addressed. Firstly, its single-center design and relatively small sample size may introduce inherent selection bias. Secondly, the modest number of subjects with low QFR in our study, accounting for 28 patients or 20.3 % of the total, suggests that our population primarily exhibited a relatively moderate burden of epicardial stenosis. Consequently, the generalizability of our study's findings to patients with more severe epicardial stenosis may be limited. Thirdly, the retrospective nature of the study restricted access to invasive physiological references, such as fractional flow reserve and wire-based microcirculatory index. Additionally, the accuracy of QFR computation was limited due to the retrospective approach. Fourthly, the prediction of mismatch was limited due to the low incidence rate. Fifthly, the non-linear nature of the O_2-pulse curve posed challenges in accurately quantifying its morphology, which may have influenced the precision of the derived functional index. Furthermore, our study primarily focused on a single CPET parameter related to myocardial ischemia. Future research should aim to incorporate more quantification metrics that align with the inherent characteristics of the O_2-pulse curve, potentially enhancing the accuracy of CPET in assessing myocardial ischemia. Finally, this study did not have an outcome-oriented design, thus future studies with extended clinical follow-up are necessary to investigate the prognostic significance of the O_2-pulse slope ratio.

6. Conclusion

A reduction in the O_2-pulse slope ratio indicates an elevated risk of μQFR-defined functional significance, suggesting a potential approach to detect myocardial ischemia in stable CAD patients through quantifying the morphology of O_2-pulse derived from CPET. However, given the existence of discordance and limitations, further prospective research is imperative to confirm and expand upon these preliminary findings.

CRediT authorship contribution statement

Liang Geng: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Shangwei Huang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tingting Zhang:** Funding acquisition, Formal analysis. **Jimin Li:** Data curation. **Lijie Wang:** Data curation. **Junyan Zhou:** Data curation. **Liming Gao:** Data curation. **Yunkai Wang:** Investigation. **Jiming Li:** Data curation. **Wei Guo:** Data curation. **Ying Li:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Qi Zhang:** Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101409.

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