



Original Article

# Association between pulmonary oxygen uptake on-kinetics and acute cardiovascular responses to resistance exercise in patients with coronary artery disease: a preliminary study

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**Abstract.** [Purpose] This study aimed to examine whether pulmonary oxygen uptake on-kinetics at the onset of moderate-intensity exercise can predict acute cardiovascular responses to resistance exercise. [Participants and Methods] The association between pulmonary oxygen uptake on-kinetics and acute cardiovascular responses to a single resistance exercise session was investigated in seven patients with low-risk coronary artery disease who underwent revascularization through percutaneous coronary intervention. The participants performed a cardiopulmonary exercise test on a cycle ergometer and a single resistance exercise session at 30% of maximum voluntary contraction on a bilateral leg-extension machine 1 week after surgery. We measured the ventilatory anaerobic threshold and pulmonary oxygen uptake on-kinetics during the cardiopulmonary exercise test; left ventricular ejection fraction at rest; and heart rate, systolic blood pressure, and rate pressure product during the single resistance exercise session. [Results] Pulmonary oxygen uptake on-kinetics showed a positive association with the amount of increase in systolic blood pressure and rate pressure product during the single resistance exercise session, but had no association with the amount of increase in heart rate. Ventilatory anaerobic threshold and left ventricular ejection fraction were not associated with these parameters. [Conclusion] These data suggested that pulmonary oxygen uptake on-kinetics can be a useful evaluation index for predicting acute systolic blood pressure and rate pressure product responses to low-intensity resistance exercise 1 week after percutaneous coronary intervention in patients with low-risk coronary artery disease.

**Key words:** Coronary artery disease, Oxygen uptake kinetics, Resistance exercise

*(This article was submitted Apr. 16, 2021, and was accepted May 24, 2021)*

## INTRODUCTION

Several recent meta-analyses have shown that resistance exercise (RE) is beneficial for patients with coronary artery disease (CAD), as well as those with heart failure<sup>1-4)</sup>. Furthermore, RE has been demonstrated to improve peak pulmonary oxygen uptake (peak  $\dot{V}O_{2p}$ ), muscle strength, walking capacity, and quality of life to a similar degree as aerobic exercise (AE)<sup>1-4)</sup>. The combination of RE and AE is more effective in enhancing peak  $\dot{V}O_{2p}$  and muscle strength than AE alone<sup>2, 4)</sup>. Despite this evidence, detailed recommendations for RE are not routinely incorporated in national guidelines for cardiac rehabilitation to the same level as AE prescriptions<sup>5)</sup>, decreasing the likelihood of RE benefits being achieved in clinical

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practice. In fact, a survey of 612 participants in Italy revealed that the prescription rate of RE (9.0%) was much lower than that of AE (66.7%)<sup>6</sup>. This difference could be explained by the fact that methods for determining a suitable exercise intensity have been established for AE but not for RE<sup>7-9</sup>. The exercise intensity in AE is prescribed using the ventilatory anaerobic threshold (VAT) or peak  $\text{VO}_{2p}$  determined by a cardiopulmonary exercise test before training to provide a safe and effective threshold for the cardiovascular responses to AE<sup>7, 8</sup>. To determine a safe and effective exercise intensity during RE, it would be essential to establish an evaluation index for predicting acute cardiovascular responses to RE.

RE in patients with heart disease can be considered a dynamic and non-steady-state exercise because it involves isotonic contraction, with an exercise set finishing within 3 min<sup>9, 10</sup>. During dynamic exercise, the reduction in oxygen supply to working muscles increases metabolite accumulation and evokes metaboreflex-induced increases in sympathetic nerve activity, heart rate (HR), systemic vascular resistance, and blood pressure<sup>11, 12</sup>. Given the exercise modality of RE (dynamic exercise in non-steady-state conditions) in patients with heart disease, the oxygen delivery rate to active skeletal muscles may be an appropriate index for predicting acute cardiovascular responses to RE.

Herein, we focused on the time course of  $\text{VO}_{2p}$  at exercise onset ( $\text{VO}_{2p}$  on-kinetics) determined by a constant-load exercise test at moderate intensity (i.e., exercise below the VAT). Slowed  $\text{VO}_{2p}$  on-kinetics incurs a high  $\text{O}_2$  deficit, which indicates low oxidative phosphorylation and high substrate level phosphorylation (e.g., phosphocreatine breakdown and glycogenolysis, with lactate and  $\text{H}^+$  formation)<sup>13</sup>. Although it remains unclear whether  $\text{VO}_{2p}$  on-kinetics are restricted by limitations in oxygen delivery or by oxidative inertia and utilization, several studies indicate that the oxygen delivery rate would be the limiting factor for  $\text{VO}_{2p}$  on-kinetics when it is slower than 20 s<sup>14-17</sup>. When  $\text{VO}_{2p}$  on-kinetics are limited by the oxygen delivery rate, they reflect the oxygen delivery rate to active muscles during dynamic exercise in non-steady-state conditions. A previous study in healthy young adult men whose  $\text{VO}_{2p}$  on-kinetics exceeded 20 s demonstrated a significant positive association of  $\text{VO}_{2p}$  on-kinetics with the rate of increase in blood lactate, HR, systolic blood pressure (SBP), and rate pressure product (RPP) during a single RE session<sup>18</sup>, suggesting that the  $\text{VO}_{2p}$  on-kinetics can be a useful evaluation index for predicting acute physiological responses to RE. In patients with heart disease,  $\text{VO}_{2p}$  on-kinetics can also be considered a beneficial evaluation index because they can be limited by the oxygen transport system<sup>16, 19, 20</sup>.

The aim of this study was to examine whether  $\text{VO}_{2p}$  on-kinetics in patients with CAD would be a useful evaluation index for predicting acute cardiovascular responses to RE. In addition, to determine whether  $\text{VO}_{2p}$  on-kinetics could be a superior evaluation index compared to other evaluation indexes indicating exercise tolerance or cardiac function, we also compared  $\text{VO}_{2p}$  on-kinetics with VAT and the left ventricular ejection fraction (LVEF) and assessed the strength of the association of these predictive indicators with the acute cardiovascular responses to a single RE session. This study was a preliminary study to obtain basic data for future research on relatively high-risk patients with heart disease and high-intensity RE. In this study, considering the risks of concern (e.g., abnormal blood pressure responses) during RE, we set the participants and exercise intensity as low-risk CAD and low-intensity load. We hypothesized that  $\text{VO}_{2p}$  on-kinetics in patients with low-risk CAD would be positively associated with acute cardiovascular responses to low-intensity RE, with the strength of association being the strongest for the predictive indicators.

## PARTICIPANTS AND METHODS

Seven hospitalized patients with CAD who were revascularized by percutaneous coronary intervention from September 2013 to October 2013 were recruited for the study. The patients' characteristics are listed in Table 1. The inclusion criteria were low-risk patients (class B) in the risk stratification for exercise training<sup>7</sup> and those with a preserved LVEF >45%. The exclusion criteria comprised the presence of absolute and relative contraindications to exercise testing<sup>7</sup>, pulmonary and kidney disease, and uncontrolled diabetes. The patients participated in the study approximately 1 week after surgery. They were instructed to consume a meal 2 h before the testing commenced, to avoid caffeine ingestion for 24 h prior to the test, and to take their medications as usual. All participants were given written information about the procedures of this study, and informed consent was obtained in accordance with the Declaration of Helsinki. All procedures were approved by the ethical committee of Seirei Christopher University (approval No. 12031).

The participants completed three sequential testing sessions as follows: a cardiopulmonary exercise test with a ramp protocol (session 1), a cardiopulmonary exercise test with a constant-load protocol at a moderate-intensity work rate (session 2), and a single RE test at low intensity (session 3). Each session had an interval of at least 24 h and was performed at approximately the same time of day. Sessions 1 and 2 were performed on a cycle ergometer (AEROBIKE75XL III, Konami Sports Club Co., Ltd., Tokyo, Japan) in an upright seated position. The  $\text{VO}_{2p}$  and HR were monitored continuously via a breath-by-breath gas measurement system (Aeromonitor A-E 310S, Minato Medical Science Co., Ltd., Osaka, Japan) and three-lead electrocardiography (DS-7680, Fukuda Denshi Co., Ltd., Tokyo, Japan), respectively. In session 1, a cycle ergometer ramp test (10 W/min) was performed at 50 rpm to determine the VAT. The test commenced with a 4-min rest period and 5 min of baseline cycling at 10 W before the work rate started to increase. The test was completed when the VAT was determined. In session 2, a constant-load exercise test was performed to assess  $\text{VO}_{2p}$  on-kinetics (i.e.,  $\tau\text{VO}_{2p}$  described by the phase II  $\text{VO}_{2p}$  time constant). The test commenced with a 5-min rest period and 5 min of baseline cycling at 20 W, followed by a 6-min bout at 80% of the workload corresponding to the VAT achieved during the ramp test. In session 3, a maximal voluntary contraction (MVC) test and a single RE test at 30% MVC as a low-intensity load<sup>9</sup> were conducted using a bilateral

**Table 1.** Participant characteristics

Variable	
Patients (n)	7
Male/female (n)	6/1
Age (years)	60 ± 11
Height (m)	1.7 ± 0.1
Weight (kg)	66 ± 19
BMI (kg/m <sup>2</sup> )	24 ± 5
τVO <sub>2p</sub> (s)	51 ± 24
VAT (mL/kg/min)	9.1 ± 2.4
LVEF (%)	61 ± 8
MVC (N)	34 ± 13
Diagnosis (n)	
Myocardial infarction	4
Angina	3
Pharmacotherapy (n)	
Antiplatelet agents	7
ACE inhibitors	2
ARB	3
β-adrenergic antagonists	2
Calcium antagonists	2
Statins	6
Nitrate	4
Complications (n)	
Hyperlipidemia	6
Hypertension	5
Diabetes	1

Data are presented as the mean ± standard deviation. ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; VAT: ventilatory anaerobic threshold; BMI: body mass index; LVEF: left ventricular ejection fraction; MVC: maximum voluntary contraction; τVO<sub>2p</sub>: phase II pulmonary oxygen uptake time constant.

leg-extension machine (WT-L02, Minato Medical Science Co., Ltd.) in a seated position. The MVC test was performed at isometric bilateral knee extension at 90° knee angles three times. The single RE test protocol consisted of a 5-min baseline period and three sets of 10 repetitions (2-s concentric, 1-s isometric, and 2-s eccentric) with 2-min rest periods between sets and no rest between repetitions. The participants were instructed not to hold their breath during the MVC test and exercise sessions. The HR and blood pressure were measured by an HR monitor (RS800CX, Polar Electro, Kempele, Finland) and automatic sphygmomanometer (Terumo ES-H55, Terumo Corporation, Tokyo, Japan), respectively.

Gas exchange was measured using a breath-by-breath gas measurement system, as described in an earlier study<sup>21, 22</sup>. The VO<sub>2p</sub> data for the constant-load exercise test were averaged into 5-s sampling intervals<sup>23</sup>, and then a 3-point moving average of the VO<sub>2p</sub> data was calculated. The on-transient response for the sampled VO<sub>2p</sub> data was fitted using a monoexponential model of the form  $Y(t) = Y_{Bsln} + Amp(1 - e^{-[t - TD]/\tau})$ , where  $Y(t)$  represents the VO<sub>2</sub> at any time ( $t$ );  $Y_{Bsln}$  is the baseline VO<sub>2p</sub> during 20 W cycling;  $Amp$  is the steady-state increase in VO<sub>2p</sub> above the baseline value;  $\tau$  is the time constant defined as the duration of time for VO<sub>2p</sub> to reach 63% of the steady-state increase; and  $TD$  is the time delay (so that the model is not constrained to pass through the origin). After excluding the initial 20 s (phase I) of the values, while still allowing  $TD$  to vary freely (to optimize the accuracy of parameter estimates), VO<sub>2p</sub> values were modeled from 20 s to 360 s (i.e., to 6 min) of the step transition (phase II); this ensured that each patient had attained a VO<sub>2p</sub> steady-state, yet did not bias the model fit during the on-transient. Model parameters were estimated by least-squares nonlinear regression (Microsoft Office Excel 2010, Microsoft, Tokyo, Japan), in which the best fit was defined by minimization of the residual sum of squares and minimal residual variations around the Y-axis ( $Y=0$ ). The VAT was defined as the VO<sub>2p</sub> at which CO<sub>2p</sub> production began to increase out of proportion relative to VO<sub>2p</sub> with a systematic rise in the minute ventilation-to-VO<sub>2p</sub> ratio and end-tidal partial pressure of O<sub>2p</sub>, whereas the minute ventilation-to-VO<sub>2p</sub> ratio and end-tidal partial pressure of CO<sub>2p</sub> were stable<sup>24</sup>. The LVEF at rest was evaluated using an echocardiogram, and data were obtained from medical records. The HR (R-R interval) was recorded

continuously throughout a single RE test at 30% MVC (the baseline and exercise session) at a 1,000-Hz sampling rate. The time series of R-R intervals were downloaded to the Polar ProTrainer 5 software (Polar Electro, Kempele, Finland), and was further converted to HR every 10 s using the MemCalc system (MemCalc™/Tarawa, Suwa Trust, Tokyo, Japan). Baseline and exercise values were defined as the average value for 2 min prior to exercise and 50 s during exercise, respectively. Brachial artery SBP and diastolic blood pressure (DBP) were measured at baseline (from 3 min to 2 min prior to exercise) and during the final 30 s of each set. All measurements were performed by the same evaluator in accordance with the guidelines of the American Heart Association<sup>25</sup>). The three MVC values (N) at isometric bilateral knee extension were averaged. The HR, SBP, and DBP across all RE sessions (three sets) were averaged for each parameter to provide an exercise value. The RPP was calculated using the formula  $RPP = HR \times SBP$ . The amount of increase ( $\Delta$ ) in each parameter was calculated by subtracting the resting value from the exercise value.

All analyses were performed using the IBM SPSS version 26 statistical software package (IBM Corp., Armonk, NY, USA). Results are presented as means  $\pm$  standard deviations. The Shapiro-Wilk test was used to test the normality of the distributions of the continuous variables. Based on the results, a paired t-test or Wilcoxon signed-rank test was performed to detect significant changes in the HR, SBP, DBP, and RPP from baseline to exercise. Pearson's correlation coefficients were used to assess the association of predictive indicators ( $\tau VO_{2p}$ , VAT and LVEF) with the amount of increase in cardiovascular parameters significantly increased during a single RE session. A p-value  $<0.05$  was considered to reflect statistical significance.

## RESULTS

Participant characteristics are displayed in Table 1. Table 2 shows the values of the cardiovascular parameters at rest and during exercise in a single RE session and the relative increases in these parameters. A single RE session led to significant increases in the HR, SBP, and RPP compared with the resting values, but no significant increase in DBP. Correlation coefficients and p-values between predictive indicators and the amount of increase in cardiovascular parameters ( $\Delta HR$ ,  $\Delta SBP$ , and  $\Delta RPP$ ) during a single RE session are presented in Table 3.

## DISCUSSION

We examined the association between  $\tau VO_{2p}$  and acute cardiovascular responses to a low-intensity RE in patients with low-risk CAD. The main results showed that  $\tau VO_{2p}$  was associated with  $\Delta SBP$  and  $\Delta RPP$ , but not with  $\Delta HR$  during a low-intensity RE. Furthermore, the VAT and LVEF were not associated with all of these parameters. Therefore, our results suggested that  $\tau VO_{2p}$  can be a useful evaluation index for predicting acute SBP and RPP responses to low-intensity RE in patients with low-risk CAD.

**Table 2.** Cardiovascular parameters during a single resistance exercise session

	Rest	Exercise	$\Delta$ (exercise-rest)
HR (beats/min)	66 $\pm$ 9	71 $\pm$ 8*	6 $\pm$ 5
SBP (mmHg)	133 $\pm$ 11	148 $\pm$ 15*	15 $\pm$ 14
DBP (mmHg)	78 $\pm$ 10	92 $\pm$ 17	14 $\pm$ 17
RPP ( $\times 10^3$ beats/min $\cdot$ mmHg)	8.7 $\pm$ 0.8	10.5 $\pm$ 1.4*	1.8 $\pm$ 0.6

Values are presented as the mean  $\pm$  standard deviation. \* $p < 0.05$  for rest vs. exercise.

$\Delta$  stands for the amount of increase in cardiovascular parameters during a single resistance exercise session. DBP: diastolic blood pressure; HR: heart rate; RPP: rate pressure product; SBP: systolic blood pressure.

**Table 3.** Correlation coefficients and p-values between predictive indicators and the amount of increase in cardiovascular parameters during a single resistance exercise session

	$\tau VO_{2p}$ (s)		VAT (mL/kg/min)		LVEF (%)	
	r	p	r	p	r	p
$\Delta HR$	-0.57	0.18	0.49	0.27	0.33	0.47
$\Delta SBP$	0.80	0.03	-0.27	0.56	-0.16	0.73
$\Delta RPP$	0.76	0.048	0.01	0.99	0.05	0.91

$\Delta$  stands for the amount of increase in cardiovascular parameters during a single resistance exercise session. HR: heart rate; LVEF: left ventricular ejection fraction; RPP: rate pressure product; SBP: systolic blood pressure;  $\tau VO_{2p}$ : phase II pulmonary oxygen uptake time constant; VAT: ventilatory anaerobic threshold.

Several studies have shown that the oxygen transport system is the limiting factor of  $\tau\text{VO}_{2p}$  only when it exceeds 20 s<sup>14–17</sup>). In the present study, given that the  $\tau\text{VO}_{2p}$  in patients with CAD exceeded 20 s, it reflected the rate of oxygen delivery to active muscles during dynamic exercise in non-steady-state conditions. In this context, patients with a slow  $\tau\text{VO}_{2p}$  would be unable to accelerate the provision of oxygen to working muscles during a single RE session, leading to exaggerated increases in muscle metabolites and metaboreflex-induced increases in SBP responses. Ultimately, this results in a significant association between  $\tau\text{VO}_{2p}$  and  $\Delta\text{SBP}$ .

In contrast,  $\tau\text{VO}_{2p}$  was not associated with  $\Delta\text{HR}$  during a single RE session. This study included patients with diabetes who may have autonomic dysfunction and were taking  $\beta$ -adrenergic antagonists. Thus, the  $\Delta\text{HR}$  was not likely to increase with the degree of metaboreflex activity, resulting in no association between  $\tau\text{VO}_{2p}$  and  $\Delta\text{HR}$ . However, our results should be interpreted with caution because of the small sample size. The  $\Delta\text{RPP}$  was determined by the  $\Delta\text{HR}$  and  $\Delta\text{SBP}$ . The absolute value of  $\Delta\text{SBP}$  was greater than that of  $\Delta\text{HR}$  (Table 2). That is, the  $\Delta\text{SBP}$  can more strongly affect  $\Delta\text{RPP}$  than the  $\Delta\text{HR}$ , resulting in a significant association between  $\tau\text{VO}_{2p}$  and  $\Delta\text{RPP}$ . These results suggested that  $\tau\text{VO}_{2p}$  in patients with low-risk CAD can be a useful evaluation index for predicting acute SBP and RPP responses to low-intensity RE.

In contrast to the results for  $\tau\text{VO}_{2p}$ , neither the VAT nor LVEF was associated with the acute cardiovascular responses during a single RE session. This can be explained by the fact that the VAT and LVEF are not capable of reflecting the oxygen provision ability during dynamic exercise in non-steady-state conditions. The measurement condition of VAT and LVEF is different from the exercise modality of RE (VAT, ramp; LVEF, rest; RE, non-steady-state)<sup>7, 8</sup>). Moreover, the VAT is not only regulated by central factors but also by peripheral factors, including the skeletal muscle mass and oxidative capacity of muscles<sup>26–29</sup>). Hence, it is biologically plausible that neither the VAT nor LVEF should be suitable as an evaluation index for predicting acute cardiovascular responses to low-intensity RE.

Our study has some limitations. First, the sample size is small. Second, some potential mediators that can explain the association between  $\tau\text{VO}_{2p}$  and acute cardiovascular responses to a single RE session were not measured, such as autonomic nerve activity and muscle metabolites. Third, patients included in this study were only those with low-risk CAD. Finally, this study examined the association between  $\tau\text{VO}_{2p}$  and acute cardiovascular responses only during a single RE test performed at 30% MVC. In future research, these study limitations should be addressed to confirm the validity of our findings.

In conclusion, our results suggested that  $\tau\text{VO}_{2p}$  can be a useful index for predicting acute SBP and RPP responses to low-intensity RE when evaluating patients with low-risk CAD. Future studies should address the present study limitations and then determine the reference value of  $\tau\text{VO}_{2p}$  when starting RE and increasing the exercise intensity.

### *Conflict of interest*

None.

## ACKNOWLEDGMENTS

We would like to thank all the participants for their valuable contributions to this study, as well as Editage (www.editage.jp) for English language editing.

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