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Original Article

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Partial Pressure of End-Tidal Oxygen and Blood Lactate During Cardiopulmonary Exercise Testing in Healthy Older Participants and Patients at Risk of Cardiac Disease

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Abstract

Background: The partial pressure of end-tidal oxygen ($PETO_2$) and end-tidal oxygen concentration (ETO_2) are among the indices that can be measured by exhaled gas analysis. Several observational studies have shown that skeletal muscle function is impaired in patients with cardiac disease; thus, the assessment of skeletal muscle function is important. Additionally, although it has recently been suggested that the difference in $PETO_2$ from rest to the ventilatory anaerobic threshold (VAT) reflects oxygen availability in peripheral factors, primarily skeletal muscle, the evidence for this is not well established. Therefore, we hypothesized and investigated whether increased blood lactate (BLa) levels, resulting from decreased skeletal muscle and mitochondrial oxygen availability, and $PETO_2$ dynamics during cardiopulmonary exercise testing (CPET) would be related.

Methods: All participants performed the symptomatic limited CPET, and their BLa levels were measured. The difference in $PETO_2$ and ETO_2 from rest to VAT determined by the V-slope method ($\Delta PETO_2$ and ΔETO_2) was calculated and compared with the increase in BLa due to exercise testing.

Results: We recruited 22 healthy older participants (nine males; 69.4 ± 6.8 years) and 11 patients with cardiovascular risk (eight males; 73.0 ± 8.8 years). $\Delta PETO_2$ and ΔETO_2 did not differ between the two groups (P = 0.355 and P = 0.369, respectively), showing no correlation between increase in BLa from rest to VAT, but were significantly correlated with an increase in BLa from rest to the end of exercise ($\Delta PETO_2$, P = 0.030; ΔETO_2, P = 0.029). The correlation was particularly pronounced among those at cardiovascular risk ($\Delta PETO_2$, P = 0.012; ΔETO_2, P = 0.011).

Conclusions: $\Delta PETO_2$ and ΔETO_2 from rest to VAT during CPET may be useful as indices reflecting skeletal muscle oxygen utilization capacity.

Keywords: End-tidal oxygen; Blood lactate; Cardiopulmonary exercise testing; Cardiovascular disease; Incremental exercise; Older population

Introduction

For accurate exercise prescription and cardiorespiratory health assessment, cardiopulmonary exercise testing (CPET) using a respiratory gas analyzer system has become the gold standard protocol in research and clinical practice to quantify main aerobic parameters (e.g., maximal peak oxygen uptake (VO_2), ventilatory anaerobic threshold (VAT), and respiratory compensation point (RCP)) [1]. In addition, the partial pressure of end-tidal oxygen ($PETO_2$) and end-tidal oxygen concentration (ETO_2) are among the indicators that can be measured by exhaled gas analysis.

When the oxygen demand of exercising muscles increases, blood flow to these muscles increases and oxygen extraction from the blood by the muscles increases, which leads to a decrease in the partial pressure of oxygen in the blood that returns to the lungs [2]. This, in turn, leads to a decrease in $PETO_2$ during exercise. Thus, a greater decrease in $PETO_2$ from rest to exercise would indicate greater oxygen extraction and utilization by the muscles.

In general, skeletal muscle oxygen utilization refers to the amount of oxygen supplied to and utilized by muscles during physical activity and is usually measured by methods such as near infrared spectroscopy (NIRS) and muscle oxygen saturation (SmO_2) monitoring [3, 4]. In addition, differences in $PETO_2$ from rest to VAT ($\Delta PETO_2$) reflect oxygen extraction capacity in peripheral factors, such as the skeletal muscles [5-7]. Blood lactate (BLa) exists as an intermediate metabolite between glycolysis and mitochondrial oxygen utilization [8], and decreased skeletal muscle and mitochondrial oxygen availabil-

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ity may indicate increased BLa [9, 10]. Although $\Delta PETO_2$ and BLa are not directly related, both are indicators of different aspects of muscle metabolism during exercise. $\Delta PETO_2$ reflects the extraction and utilization of oxygen by muscle [5-7], while BLa reflects the accumulation of lactic acid in the blood, a byproduct of anaerobic metabolism [11]. Additionally, various risk factors for cardiovascular disease have been reported to cause a decrease in type 1 fibers, leading to impaired skeletal muscle function [12, 13]. It is conceivable that a decrease in skeletal muscle oxygen availability would result in an early addition of anaerobic metabolism in response to increased exercise intensity, leading to a greater accumulation of lactate, while $\Delta PETO_2$ would decrease.

We hypothesized that low $\Delta PETO_2$, which indicates peripheral skeletal muscle oxygen utilization during CPET, would result in higher BLa at the end of exercise, and that this would be more pronounced in individuals at risk for cardiac disease. We, therefore, aimed to clarify the relationship between $\Delta PETO_2$ and BLa during CPET in healthy older participants and patients with risk for cardiac disease close to the age of eligibility for cardiac rehabilitation [14-16]. The results of this study will provide evidence that $\Delta PETO_2$ is an indicator of skeletal muscle oxygen utilization capacity and will provide a noninvasive indicator of changes in skeletal muscle function with exercise training.

Materials and Methods

Participants

We enrolled participants aged between 60 and 80 years during the period May 1, 2016, to April 30, 2019. The recruitment process resulted in 11 patients who were currently taking medication for either cardiovascular diseases (n = 5) or cardiovascular risk factors (n = 6), forming group P, which had an average age of 72.6 ± 8.5 years and consisted of nine males. Among these patients, the cardiovascular disease etiologies included coronary artery disease post-coronary artery bypass graft surgery (n = 2), myocardial infarction (n = 1), and valvular heart disease (n = 2), while the cardiovascular risk factors included hypertension (n = 11), impaired glucose tolerance or diabetes mellitus (n = 2), and hyperlipidemia (n = 8). For comparison purposes, 22 healthy participants were recruited, forming group H, and matched the age range of group P, with an average age of 69.3 ± 6.7 years and nine male participants (Table 1).

We excluded patients with recent changes in medication within 6 months, recent infection within 2 weeks, body temperature exceeding 37.5 °C, chronic atrial fibrillation or flutter, permanent pacemakers, and orthopedic conditions that could hinder exercise testing. Participants who were on warfarin or other anticoagulants and metformin for diabetes were also excluded. The cases and measurement records for this study were collected from participants in a previous study [17].

Exercise testing

CPET was performed using a stationary bicycle (Strength-Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan) and a breath-by-breath gas analyzer (AE-300S; Minato Ikagaku Co., Tokyo, Japan). Symptomatic maximal exercise was performed using a ramp protocol of 10 W/min (incremental exercise). After 2 min rest (sitting on the stationary bicycle), warm-up exercises were performed for 2 min at 10 W. We used 10-s average data for all analyses. The output was obtained using a gas analyzer system.

VAT determination

We determined VAT during incremental exercise testing, visually determined using the modified V-slope method described by Sue et al [18], a modification of the method described by Beaver et al [19], as previously published [20, 21].

BLa measurement

Blood was sampled using a finger prick test. A topical vasodilator (Finalgon cream, nonivamide butoxyethyl; Boehringer Ingelheim, Gaithersburg, MD) was applied to three fingers of the left hand (second, third, and fourth). The cream was removed after 10 min, and the entire left hand, including the distal part of the forearm, was placed in a water bath (at 43 - 45 °C) for 10 min [22, 23]. The BLa levels were determined using Lactate Pro LT-1730 (Arkray, Kyoto, Japan), calibrated using a strip before each exercise session. Blood samples were collected every minute during the ramp exercise.

$PETO_2$ and ΔETO_2

Rest $PETO_2$ and ETO_2 were recorded as the mean value of the last half 1 min at the 2 min rest period in CPET. $\Delta PETO_2$ was the difference between VAT $PETO_2$ and rest $PETO_2$. ΔETO_2 was calculated in the same way.

Rate of perceived exertion and miscellaneous measures

The rate of perceived exertion was measured using the Borg scale. Left ventricular ejection fraction was determined using the Teichholz method. Brain natriuretic peptide levels were determined using a chemiluminescent enzyme immunoassay.

Statistical analysis

Data are presented as mean ± standard deviation (SD) and 95% confidence intervals. Unpaired data were analyzed using Student's *t*-test. Paired data were analyzed using paired *t*-tests. Comparisons of BLa, $PETO_2$, and ETO_2 between the two groups were performed using a repeated two-way analysis of variance (ANOVA). Plots of the $\Delta PETO_2$, ΔETO_2, and BLa were linearly regressed, and regression equations and coefficients were calculated. The 95% confidence intervals were

Table 1. Data of Participants' Clinical Characteristics

Characteristics	Healthy group (H: n = 22)	Patient group (P: n = 11)	P value
Age, years	69.6 ± 6.6	72.6 ± 8.5	NS
	66.8 - 72.4	67.6 - 77.6	
Sex	M: 9, F: 13	M: 9, F: 2	NS
Height, cm	158.5 ± 6.4	164.8 ± 3.6	0.005
	155.9 - 161.2	162.7 - 167.0	
Body weight, kg	56.0 ± 8.4	66.1 ± 10.5	0.005
	52.5 - 59.5	59.9 - 72.3	
BMI, kg/m^2	22.2 ± 2.1	24.4 ± 4.1	NS
	21.3 - 23.1	21.9 - 26.8	
CTR, %		48.6 ± 4.3	
		45.1 - 50.7	
BNP, pg/dL		79.8 ± 131.6	
		-0.8 - 148.6	
eGFR, mL/min/1.73 m^2		63.7 ± 16.5	
		54.0 - 73.5	
Hb, g/dL		13.8 ± 0.9	
		13.2 - 14.3	
Ht, %		41.7 ± 2.6	
		40.1 - 43.2	
LVEF, %		68.3 ± 14.1	
		60.2 - 76.0	
Comorbidity			
Hypertension, n (%)	0 (0)	11 (100)	
Dyslipidemia, n (%)	0 (0)	8 (73)	
Impaired glucose tolerance, n (%)	0 (0)	2 (18)	
Obesity, n (%)	2 (9)	4 (36)	
Medication			
CCB, n (%)	0 (0)	7 (63.6)	
ACEI/ARB, n (%)	0 (0)	5 (45.5)	
Beta blocker, n (%)	0 (0)	3 (27.3)	
Statin, n (%)	0 (0)	6 (54.5)	
Antilipidemic, n (%)	0 (0)	3 (27.3)	
Nitrate, n (%)	0 (0)	3 (27.3)	
Antiplatelet, n (%)	0 (0)	6 (54.5)	
Anticoagulant, n (%)	0 (0)	2 (18.2)	
DPP-4 inhibitor, n (%)	0 (0)	2 (18.2)	
SGLT2 inhibitor, n (%)	0 (0)	1 (9.1)	

Data are presented as mean ± standard deviation (SD) and 95% confidence intervals, and obesity was defined as BMI > 25 kg/m^2. No significant differences in clinical characteristics, such as age and BMI, were observed between the two groups. H: healthy group; P: patients group; CTR: cardiothoracic ratio; BMI: body mass index; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; Ht: hematocrit; LVEF: left ventricular ejection fraction; CCB: calcium channel blocker; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; DPP-4: dipeptidyl peptidase-4; SGLT2: sodium glucose cotransporter 2; NS: not significant; M: male; F: female.

also calculated to determine the relationship between $\Delta PETO_2$, ΔETO_2, and BLa. Statistical analyses were performed with Statistics for Excel 2012 (Social Survey Research Information Co., Tokyo, Japan).

Ethical considerations

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Institutional Review Board of Sapporo Ryokuai Hospital (approval number: 19-1). Informed consent was obtained from all participants permission in writing provided for publication of this report. The authors confirm that there is no identifying information of the participants in the manuscript and that the information has been fully anonymized. Furthermore, the authors affirm that all mandatory health and safety procedures were observed while conducting the experimental work reported in this paper.

Results

The clinical characteristics of the participants are summarized in Table 1. Group P had a higher proportion of males, with significantly higher mean height and weight, than group H.

Change of $PETO_2$, ETO_2, and BLa

The changes over time in $PETO_2$, ETO_2, and BLa during the CPET are shown in Table 2. No significant differences were found between the two groups. There were also no significant differences in $\Delta PETO_2$ and ΔETO_2 between the two groups ($\Delta PETO_2$ (at rest) H: -6.21 ± 3.13 (-4.91 to -7.52) mm Hg, P: -5.21 ± 3.13 (-3.36 to -7.06) mm Hg, P = 0.355; ΔETO_2 (at rest) H: -0.89±0.45% (-0.70 to -1.07), P: -0.75±0.45% (-0.48 to -1.01), P = 0.369).

Furthermore, there were no significant differences in ΔBLa from rest to VAT (VAT - rest; H: 0.35 ± 0.31 (0.22 - 0.48) mmol/L, P: 0.44 ± 0.31 (0.25 - 0.62) mmol, P = 0.483), rest to peak (peak - rest; H: 4.14 ± 2.28 (3.19 - 5.09) mmol/L, P: 4.85 ± 2.28 (3.43 - 6.26) mmol, P = 0.321), and VAT to peak (peak - VAT; H: 3.79 ± 2.25 (2.85 - 4.73) mmol/L, P: 4.39 ± 2.25 (3.00 - 5.79) mmol, P = 0.405).

$\Delta PETO_2$, ΔETO_2, and BLa

There was a significant correlation between $\Delta PETO_2$ and ΔBLa (peak - rest) ($r = 0.428$ ($0.100 \leq \rho \leq 0.673$), P = 0.014), $\Delta PETO_2$, and ΔBLa (peak - AT) ($r = 0.436$ ($0.109 \leq \rho \leq 0.678$), P = 0.012). ΔETO_2 showed a significant correlation as well (ΔBLa (peak - rest); $r = 0.431$ ($0.102 \leq \rho \leq 0.674$), P = 0.014, ΔBLa (peak - AT); $r = 0.440$ ($0.114 \leq \rho \leq 0.681$), P = 0.013).

Also, separating the healthy older and those at risk for cardiac disease, no correlation was observed in the healthy older; however, a significant correlation with $\Delta PETO_2$, ΔETO_2, and ΔBLa was observed in those at risk for cardiac disease (Fig. 1) ($\Delta PETO_2$: P; $r = 0.736$ ($0.243 \leq \rho \leq 0.927$), P = 0.012, H; $r = 0.205$ ($-0.237 \leq \rho \leq 0.577$), P = 0.377, P vs. H; P = 0.082, ΔETO_2: P; $r = 0.739$ ($0.250 \leq \rho \leq 0.928$), P = 0.011, H; $r = 0.205$ ($-0.237 \leq \rho \leq 0.577$), P = 0.376, P vs. H; P = 0.079).

Discussion

$\Delta PETO_2$ and ΔETO_2 did not differ between the two groups and were not correlated with an increase in BLa from rest to VAT, but they were significantly correlated with an increase in BLa from rest to the end of exercise. The correlation was particularly pronounced among those at cardiovascular risk. Therefore, $\Delta PETO_2$ and ΔETO_2 from rest to VAT may be useful as indices reflecting skeletal muscle oxygen utilization capacity. To the best of our knowledge, this is one of the few studies to confirm the relationship between the change of BLa levels, ETO_2, and $PETO_2$ during incremental exercise testing in healthy older adults and patients with cardiovascular disease/risk factors. To date, these results have not been reported in healthy older adults or patients with cardiovascular risk.

$PETO_2$ decreases from rest to VAT. This is due to an increase in oxygen uptake with exercise, an increase in minute ventilation, and an increase in oxygen utilization in the alveoli due to improved gas exchange efficiency, resulting in a decrease in oxygen in exhaled breath. Once VAT is reached, $PETO_2$ begins to increase as the rate of anaerobic metabolism increases and the minute ventilation rate increases beyond oxygen uptake (i.e., ventilation increases beyond oxygen demand, and oxygen not used for gas exchange is returned to the exhaled breath). In the present study, $PETO_2$ and ETO_2 were significantly higher at VAT in patients with cardiovascular risk compared to healthy subjects. In addition, $PETO_2$ and ETO_2 from rest to VAT ($\Delta PETO_2$ and ΔETO_2) tended to be lower, although the differences were not significant.

Various risk factors for cardiovascular disease have been reported to cause a decrease in type 1 fibers, leading to reduced skeletal muscle and mitochondrial function [12, 13]. Furthermore, progression to heart failure further reduces skeletal muscle and mitochondrial function [24-26]. Therefore, $\Delta PETO_2$ and ΔETO_2 may gradually decrease with the progression of heart disease and the onset and severity of heart failure. Since the present study included well-controlled patients with risk of cardiac disease and healthy subjects, $\Delta PETO_2$ was comparable to that of the mild disease group in a previous study [6]. Therefore, it is possible that skeletal muscle function or skeletal muscle and mitochondrial oxygen utilization capacity was not as impaired as in the medium to severe disease group of the previous study. Alternatively, the limited number of cases in the present study may have resulted in the absence of statistically significant differences. The knowledge of the dynamics of $PETO_2$ during the incremental exercise used in the present study is scarce, and it is desirable to continue the investigation and deepen the knowledge by including more severe cases of impaired cardiac function.

As exercise intensity increases, the exercising muscles produce the energy required for exercise. At exercise inten-

Table 2. Data of End-Tidal Oxygen Concentration and Blood Lactate in CPET

	Group	Rest	WU	VAT	RCP	Peak
VO_2, mL/min	H	235 ± 41	432 ± 67[a]	683 ± 131[a]	1,147 ± 253[a]	1,370 ± 312[a]
		218 - 253	404 - 460	628 - 739	1,036 - 1,260	1,240 - 1,504
	P	248 ± 50	432 ± 99[a]	678 ± 177[a]	1041 ± 275[a]	1,310 ± 319[a]
		218 - 277	374 - 491	574 - 782	879 - 1,204	1,121 - 1,498
VO_2/W, mL/kg/min	H	4.3 ± 0.8	7.8 ± 1.4[a]	12.4 ± 2.7[a]	20.4 ± 3.5[a]	24.5 ± 4.2[a]
		3.9 - 4.6	7.2 - 8.4	11.3 - 13.6	18.9 - 22.0	22.7 - 26.3
	P	3.8 ± 0.6	6.5 ± 1.0[a]	10.2 ± 1.5[a, b]	15.6 ± 2.3[a, b]	19.7 ± 3.6[a, b]
		3.4 - 4.1	6.0 - 7.1	9.3 - 11.1	14.2 - 16.9	17.6 - 21.8
RER	H	0.84 ± 0.07	0.85 ± 0.07	0.85 ± 0.05	1.06 ± 0.04[a]	1.14 ± 0.11[a]
		0.81 - 0.87	0.82 - 0.88	0.83 - 0.88	1.04 - 1.08	1.10 - 1.19
	P	0.87 ± 0.06	0.88 ± 0.08	0.87 ± 0.07	1.04 ± 0.11[a]	1.16 ± 0.13[a]
		0.83 - 0.90	0.83 - 0.92	0.83 - 0.92	0.98 - 1.11	1.08 - 1.25
HR, bpm	H	68.0 ± 10.6	77.5 ± 9.4[a]	91.9 ± 12.6[a]	121.9 ± 16.6[a]	143.6 ± 19.8[a]
		63.6 - 72.4	73.5 - 81.4	86.6 - 97.2	114.4 - 129.4	134.9 - 152.3
	P	66.6 ± 7.4	75.1 ± 8.7[a]	86.2 ± 9.4[a]	111.5 ± 15.4[a]	131.5 ± 17.7[a]
		62.2 - 71.0	70.0 - 80.2	80.7 - 91.8	102.5 - 120.6	121.0 - 141.9
WR, watt	H			44 ± 11	82 ± 20	102 ± 21
				39 - 48	73 - 90	93 - 111
	P			38 ± 14	75 ± 18	101 ± 23
				30 - 47	65 - 86	88 - 115
$PETO_2$, mm Hg	H	105.5 ± 4.8	102.6 ± 5.0[a]	99.3 ± 4.6[a]	105.0 ± 4.2	112.0 ± 5.6[a]
		103.5 - 107.5	100.5 - 104.6	97.4 - 101.2	103.1 - 106.9	109.7 - 114.3
	P	106.3 ± 4.4	105.0 ± 5.1[b]	101.1 ± 6.3[a]	105.0 ± 7.7	113.2 ± 7.6[a]
		103.7 - 108.9	102.0 - 108.0	97.3 - 104.8	100.4 - 109.6	108.7 - 117.7
ETO_2, %	H	15.0 ± 0.7	14.6 ± 0.7[a]	14.1 ± 0.7[a]	14.9 ± 0.6	15.9 ± 0.8[a]
		14.7 - 15.3	14.3 - 14.9	13.8 - 14.4	14.6 - 15.2	15.6 - 16.2
	P	15.2 ± 0.6	15.0 ± 0.7[b]	14.4 ± 0.9[a, b]	15.0 ± 1.0	16.2 ± 1.0[a]
		14.8 - 15.5	14.6 - 15.4	13.9 - 14.9	14.4 - 15.6	15.6 - 16.8
Bla, mmol/L	H	1.15 ± 0.32		1.50 ± 0.28[a]		5.29 ± 1.72[a]
		1.02 - 1.28		1.38 - 1.62		4.57 - 6.01
	P	1.35 ± 0.29		1.79 ± 0.40[a]		5.91 ± 2.48[a]
		1.19 - 1.52		1.55 - 2.03		4.45 - 7.37

[a]Significant (P < 0.05) vs. rest. [b]Significant (P < 0.05) vs. group H. Data are presented as mean ± standard deviation (SD) and 95% confidence intervals. Both $PETO_2$ and ETO_2 were significantly lower at VAT compared to those at rest. In addition, in ETO_2, ETO_2 during VAT was significantly higher in the patient group than in the healthy group, and $PETO_2$ showed a similar trend. H: healthy group; P: patients group; VO_2: oxygen uptake; VO_2/W: oxygen uptake per weight; RER: respiratory exchange ratio; HR: heart rate; WR: work rate; ETO_2: end-tidal oxygen concentration; $PETO_2$: partial pressure of end-tidal oxygen; BLa: blood lactate; WU: warming-up; VAT: ventilatory anaerobic threshold; RCP: respiratory compensation point; bpm: beats per minute; CPET: cardiopulmonary exercise testing.

sities below VAT, the electron transport chain is the main source of energy production, and as the exercise intensity increases and becomes higher than the VAT, the rate of energy production by the glycolytic pathway increases. This increased lactate produced by the exercising muscles exceeds the buffering capacity of the organism, resulting in increased BLa levels. Lactate produced by exercise has recently been shown to have a variety of positive effects on the body [27]. However, this BLa level is greatly influenced by the amount of lactate produced by the activity of the glycolytic system, skeletal muscle oxygen utilization capacity, and lactate clearance by mitochondrial function [8, 28]. Decreased skeletal muscle and mitochondrial oxygen utilization capacity facilitates the production of lactate to provide the energy re-

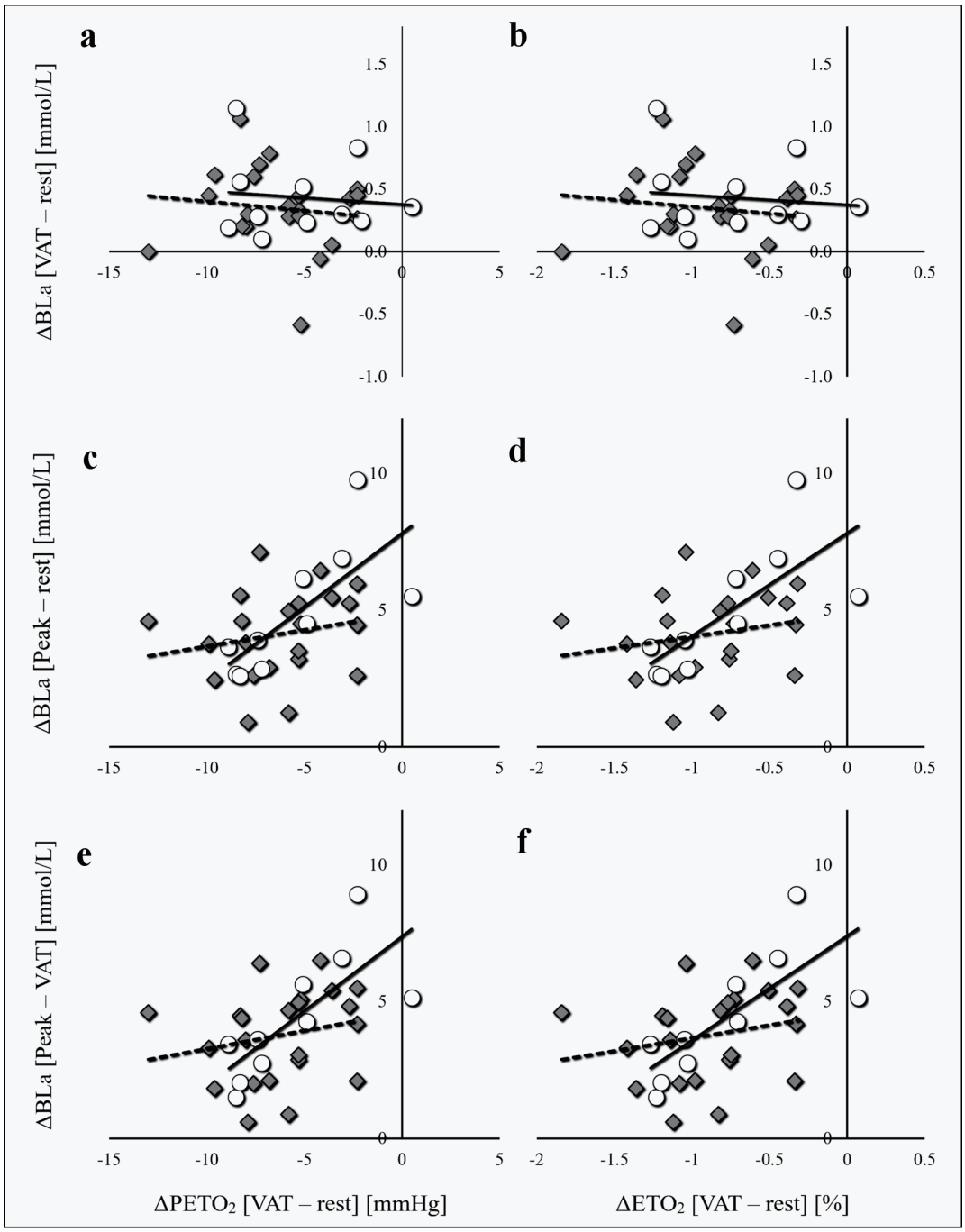

Figure 1. Relationship between $\Delta PETO_2$, ΔETO_2, and BLa. The diamond (◊) and dotted line indicates healthy subjects, and the circle (○) and straight line indicate patients with cardiac risks. $\Delta PETO_2$ and ΔETO_2 were not correlated with BLa from rest to VAT (BLa (VAT - rest)) in both groups (a, b). In subjects at risk for cardiac disease, $\Delta PETO_2$ from rest to VAT ($\Delta PETO_2$) showed a significant correlation with the increase in BLa from rest to peak (ΔBLa (peak - rest)) (c). $\Delta PETO_2$ and the increase in BLa from VAT to peak (ΔBLa (peak - VAT)) also showed a significant correlation (e). ΔETO_2 also showed similar associations (d, f). ETO_2: end-tidal oxygen concentration; $PETO_2$: partial pressure of end-tidal oxygen; BLa: blood lactate; VAT: ventilatory anaerobic threshold.

quired for exercise. In addition, patients with cardiac disease are more likely to have increased BLa levels during exercise [29]. Moreover, progression of renal dysfunction or anemia enhances glycolytic system activity, resulting in an increase in lactate production [30, 31]. However, since renal dysfunction or anemia was virtually absent in the patients with cardiac risk in the present study, increased lactate production due to glycolytic pathway activity was unlikely to occur, suggest-

ing that decreased lactate clearance associated with impaired skeletal muscle mitochondrial function was responsible for the increased BLa levels (lactate shuttles are used as an energy substrate by skeletal muscle type I fibers in other parts of the body). This would suggest that BLa was slightly higher in the patients with cardiac risk compared to the healthy group at VAT, and that BLa was significantly higher at peak exercise. Thus, $\Delta PETO_2$ or ΔETO_2 in patients with no or mildly impaired renal function during incremental exercise was associated with increased BLa levels as well as skeletal muscle oxygen utilization capacity.

However, $PETO_2$ has been shown to be affected by changes in measured altitude or ventilation [32]. Since no differences were observed in the relationship of $\Delta PETO_2$ and ΔETO_2 to changes in BLa, neither indicator requires consideration in a standard environment, but care should be taken in the handling of values and interpretation depending on the environment. In addition, since $\Delta PETO_2$ and ΔETO_2 estimate skeletal muscle oxygen utilization capacity indirectly via the exhaled gas, they are not as accurate as direct measurements of muscle oxygenation such as NIRS and SmO_2 monitoring, and their reliability may be increased when used in conjunction with these instruments [33, 34]. Furthermore, we believe that confirmation of underlying disease will be important in diseases such as chronic obstructive pulmonary disease (COPD), where the dead space is increased, because the respiratory state may be easily affected.

There are some limitations to this study. First, the number of cases is small. Therefore, the characteristics of the disease have not been adequately investigated. Second, the oxygen utilization capacity of skeletal muscle has not been directly examined. Therefore, skeletal muscle oxygen utilization has been assessed indirectly and other factors related to exhaled gas analysis and BLa levels have not been evaluated.

Conclusions

The amount of change in $PETO_2$ from rest to VAT ($\Delta PETO_2$) was associated with the amount of increase in BLa during the subsequent incremental exercise. $\Delta PETO_2$ and ΔETO_2 from rest to VAT may be useful as indices reflecting skeletal muscle oxygen utilization capacity.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Informed consent was obtained from all participants' permission in writing provided for publication of this report.

Author Contributions

KK and MA developed the study concept and were involved in its design and implementation. KK delivered program content to the participants, acquired data, analyzed the data, and prepared the manuscript. MA drafted the manuscript and approved the final draft. All the authors have read and approved the final version of the manuscript.

Data Availability

The dataset used in this study is available from the corresponding author upon request.

Abbreviations

VAT: ventilatory anaerobic threshold; CPET: cardiopulmonary exercise testing; VO_2: oxygen uptake; ETO_2: end-tidal oxygen concentration; $PETO_2$: partial pressure of end-tidal oxygen

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