Oxidative Capacity of the Skeletal Muscle and Lactic Acid Kinetics During Exercise in Healthy Subjects and Patients with COPD

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Abstract [Background] In patients with chronic obstructive pulmonary disease (COPD), early lactic acidosis during exercise should be considered as playing a role in the limitation of exercise tolerance. It was hypothesized that the relationship between blood lactate concentrations (LA) and tissue oxygenation index (TOI) is available for the prediction of aerobic capacity of skeletal muscle. [Methods] Changes of LA and TOI in the vastus lateralis muscle were measured during incremental cycling exercise in 12 healthy subjects and 4 patients with COPD. The relationship between TOI and LA was examined in 12 healthy subjects and 4 COPD patients, and changes in the relationship were examined at an interval of several years (3.3 ± 1.0). [Results] (1) From the pattern LA as related to TOI, the healthy subjects were classified into the three groups. Group A ($n = 3$); LA increased slowly with a decrease in TOI. Group B ($n = 3$); LA increased steeply after the half point of maximal exercise. Group C ($n = 6$); LA increased steeply before the half point of maximal exercise. (2) In 3 patients with COPD, the relationship between TOI and LA shifted rightward at the second examination. [Conclusion] The steep increase in LA from the approximate resting value of TOI during exercise suggests that the aerobic capacity of working skeletal muscle decreased.

1 Introduction

In patients with moderate to severe COPD, the skeletal muscle dysfunction is characterized by a reduction in aerobic capacity and this should be considered as playing a role in the limitation of exercise tolerance [1]. In patients with COPD, the proportion of type I fibers (high oxidative capacity) are decreased as compared with age-matched controls [2] and early lactic acidosis occurs due to

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the reduction in aerobic capacity during exercise. Near-infrared spectroscopy (NIRS) has recently been used to evaluate muscle oxygenation [3, 4].

2 Methods

2.1 Study Design and Subjects

With reference to the assessment of exercise intolerance and the evaluation of therapeutic interventions on clinical use, the present study performed cardiopulmonary exercise testing (CPET) comprising of the imposition of symptom-limited incremental exercise in combination with comprehensive breath-by-breath monitoring. LA and TOI of the vastus lateralis muscle were measured using NIRS. The relationship between TOI and LA was analyzed retrospectively. Twelve healthy male subjects (age, 49.0 ± 17.4 years) and 4 male outpatients with stable COPD (age, 65.3 ± 12.0 years) were examined. The 12 healthy subjects were confirmed to be free of any significant cardiopulmonary disease and represented normal exercise tolerance (Table 1). COPD patients were diagnosed as mild to moderate severity (Table 2).

Table 1 Clinical characteristics of healthy subjects

Subject No.	Age (year)	BMI (kg/m^2)	%VC (%)	FEV_1% (%)	peak VO_2 (ml/min)
1	64	25.2	112.3	84.8	1361
2	60	24.2	106.1	86.4	1170
3	57	26.3	86.7	73.7	1480
4	73	24.9	135.3	114.8	1686
5	37	20.9	107.6	89.6	1733
6	63	23.6	107.6	70.8	1338
7	36	25.6	116.3	86.8	2082
8	25	22.3	123.9	93.0	1030
9	43	23.4	111.9	84.6	1374
10	34	28.4	103.4	81.1	1870
11	45	25.3	108.6	87.6	1392
12	68	25.3	90.3	79.4	1422
Mean ± SD	49.0 ± 17.4	26.3 ± 1.8	100.8 ± 9.4	82.7 ± 4.3	1561 ± 267

2.2 Exercise Test, LA Measurement, and NIRS Monitoring

An incremental symptom-limited maximal exercise test was performed using an electromagnetically braked cycle ergometer (AEROBIKE 75XL, Combi, Tokyo, Japan). The exercise protocol consisted of 3-min rest, 3-min warm-up at 10 W of 55 revolutions per minute, and then the exercise load was increased

Table 2 Clinical characteristics of COPD patients at first and second examination

Subject No.	Exam. No.	Age (year)	BMI (kg/m^2)	VC (L)	FEV_1 (L)	DLco/VA (ml/min/mmHg/L)	Peak VO_2 (ml/min)
1	1st	75	21.8	3.81	1.86	1.17	1012
	2nd	78	21.0	3.60	1.51	1.16	684
2	1st	53	17.9	4.46	2.71	2.19	1277
	2nd	55	17.8	4.26	2.82	2.13	1527
3	1st	57	22.2	4.32	1.85	2.16	1196
	2nd	61	21.8	4.15	1.80	2.02	1081
4	1st	76	23.9	4.24	2.33	2.25	1307
	2nd	80	23.5	4.43	2.19	2.00	929

incrementally by 10 W/min. Blood samples were taken directly from the earlobe and LA was measured (Pro Analyser, Arkray of the KDK Corporation; Kyoto, Japan). Blood samples were collected at rest and during exercise testing every minute and LA was measured immediately.

Oxygenation of the vastus lateralis muscle was monitored using a commercially available NIRS system (NIRO-300: Hamamatsu Photonics KK; Hamamatsu, Japan). A probe holder containing an emission probe and detection probe was attached to the left vastus lateralis muscle along the vertical axis of the thigh approximately 15 cm from the knee joint. The NIRO-300 system also measures TOI, which can be expressed as oxyhemoglobin/(oxyhemoglobin + deoxyhemoglobin) $\times$ 100 (%). TOI was measured every 2 s from 3 min before the start of exercise until the end of exercise. The variables of NIRS were recorded and analyzed using a personal computer system (PowerLab; ADInstruments Pty Ltd; Castle Hill, Australia).

3 Results

Analysis of the relationship between TOI and LA of the vastus lateralis muscle during incremental exercise tests in the healthy subjects is shown in Fig. 1. Accordingly, the pattern of LA related to TOI in the healthy subjects was classified into the three groups. Group A ($n = 3$); LA increased slowly with a decrease in TOI and the inflection point of the steep increase in LA occurred just before stopping exercise. Group B ($n = 3$); LA increased slowly with a decrease in TOI and the inflection point of the steep increase in LA occurred above the half point of maximal exercise. Group C ($n = 6$); LA increased steeply before the half point of maximal exercise and the decrease in TOI was smaller than in Group A or B.

Changes in the relationship between TOI and LA of the vastus lateralis muscle during incremental exercise tests at intervals of 3.3 $\pm$ 1.0 years in the 4 patients with COPD is shown in Fig. 2. At the second examination, LA

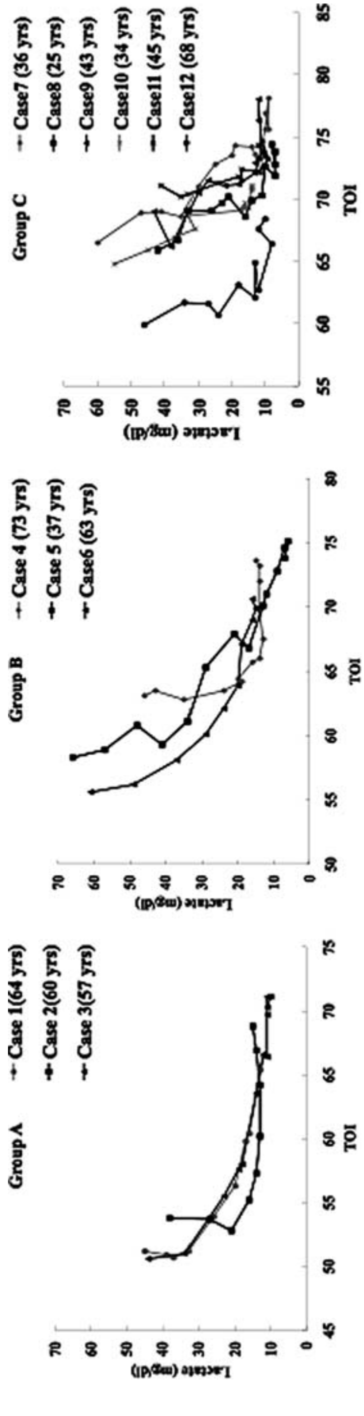

Fig. 1 Relationship between LA and TOI during incremental exercise in 12 healthy subjects

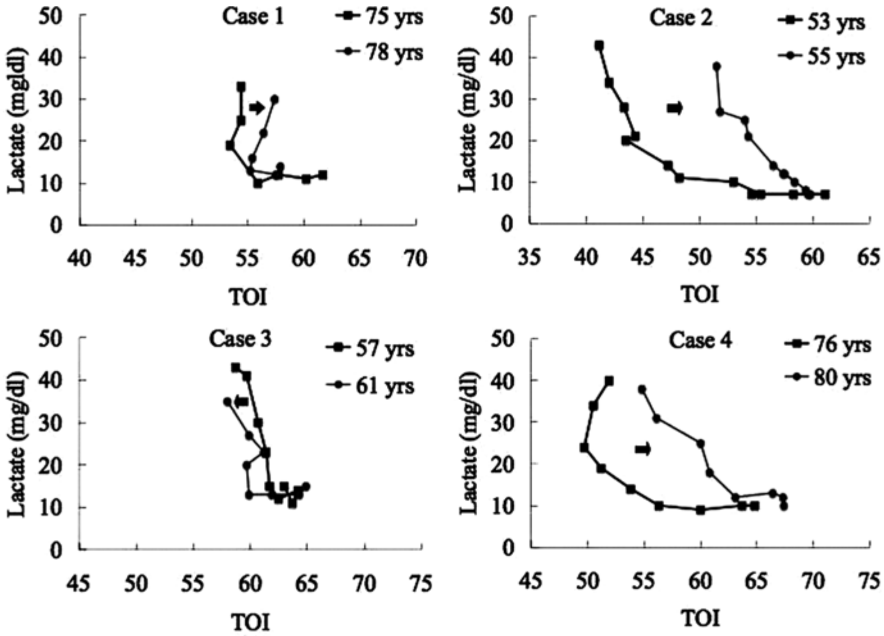

Fig. 2 Changes in relationship between LA and TOI during incremental exercise test in 4 patients with COPD

increased earlier than in the first examination, and the relationship between TOI and LA shifted rightward in 3 patients with COPD.

4 Discussion

In the present study, muscle biopsy data were not available, so the influence of muscle fiber type on oxygenation kinetics could not be determined. The kinetics of oxyhemoglobin and deoxyhemoglobin in the working skeletal muscle can be determined by the balance between O_2 utilization and muscles oxygen delivery. The NIRO-300 system also measures TOI, which is useful in the detection of muscle oxygenation changes during exercise.

We performed exercise tests using a cycle ergometer. The pedaling involves usually the vastus lateralis and the blood LA concentration reflects the production of LA in the vastus lateralis. According to the pattern of the changes in LA as related to TOI during exercise, the healthy subjects were classified into 3 groups. The subjects in Group C showed that LA increased steeply before the half point of maximal exercise and the decrease in TOI was smaller than in Groups A or B. In the healthy subjects, the increase in LA could indicate that the problem lay with skeletal muscle function rather than with O_2 delivery, because O_2 delivery to working skeletal muscles might be adequate at the early phase from the onset of exercise.

It has been shown that muscle mass decreases and the proportion of muscle fiber types change in humans. By 60–70 years of age, muscle mass decreases by 25–30% in humans, and this is mainly due to the reduction in type II fibers. In subjects older than 70 years of age, the mean area of type II fibers decreases by approximately 15% and the percentage of type II fibers decreases by 40% [1]. Therefore, it was thought that the pattern of the change in LA as related to TOI in elderly subjects was similar to Group A, i.e. resulting from the reduction in type II fibers, but the pattern of LA as related to TOI did not relate with age. There might be two reasons why the pattern of LA as related to TOI was not related to age. Firstly, changes in muscle fiber types related to age; some loss of muscle mass and strength is almost universal in older people, but varies widely between individuals, particularly in relation to habitual levels of physical activity [5]. Secondly, the difference in muscle oxygenation within the same vastus lateralis muscle; in animal models, one of the causes of regional muscle oxygenation differences is shunting of blood flow to oxidative muscle fibers compared to non-oxidative muscle fibers within the same muscle [6]. It has also been shown that NIRS measured muscle oxygenation is variable within the same muscle [7].

Compared with matched control subjects, the reduction in the proportion of type I fibers in patients with COPD was accompanied by an increase in the proportion of type IIb fibers, and the early lactic acidosis occurred due to the reduction in aerobic energy production in the early phase from the onset of exercise [1]. Figure 2 shows the changes in the relationship between TOI and LA during incremental exercise at an interval of 3.3 ± 1.0 years in COPD patients. At the second examination, LA increased earlier than in the first examination in the same way as Group C of the healthy subjects, and the relationship between TOI and LA shifted rightward in 3 patients with COPD. This suggested that the reduction in the proportion of type I fibers accompanied the increase in the proportion of type IIb fibers due to age-related changes and advances in COPD. In addition, a shift from oxidative metabolism to glycolytic metabolism occurred in skeletal muscle of the patients with COPD at low levels of exercise.

5 Conclusion

The steep increase in LA from the approximate resting value of TOI during exercise suggests that the aerobic capacity of working skeletal muscle decreases. The relationship between TOI and LA shifted rightward at interval of several years in 3 COPD patients, suggesting that the aerobic capacity of the vastus lateralis muscle decreases. Further studies are needed to examine the relationship between TOI and LA in working skeletal muscle for the assessment of endurance training efficiency.

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