Effects of Blood Gas, pH, Lactate, Potassium on the Oxygen Uptake Time Courses during Constant-Load Bicycle Exercise

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Abstract Changes in the time courses of $\dot{V}_{O_2}$ during constant-load exercise were examined in connection with other cardiorespiratory and blood chemical parameters. Eleven healthy male subjects performed a ramp exercise and three to six constant-load exercises at varying degrees of load using an electro-braked bicycle ergometer. Heart rate, ventilation, and gas exchange were measured during both types of exercise, and chemical parameters of the subject's blood (blood gas, pH, lactate, and electrolytes) were determined during two intensities of constant-load exercise. The time courses of cardiorespiratory and blood chemical data 3 min after the onset of constant-load exercise were fitted by linear regressions to see whether these parameters had reached the steady state or not. Heart rate increased significantly at a lower intensity of constant-load exercise than $\dot{V}_E$, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$. While the increase in $\dot{V}_{CO_2}$ was slower than that of $\dot{V}_{O_2}$, a definite difference in time courses was not found between $\dot{V}_E$ and $\dot{V}_{O_2}$. The time courses of changes in blood gas, pH, bicarbonate, and lactate were not correlated with those of $\dot{V}_{O_2}$. However, changes in blood potassium concentration were closely correlated with those of $\dot{V}_{O_2}$ in terms of time courses and magnitude. This suggests the possibility that blood potassium may play an important role in the control of $\dot{V}_{O_2}$ time course during constant-load exercise.

Key words: $\dot{V}_{O_2}$ time course, ventilatory threshold, blood gas, lactate, potassium.

Kinetics of oxygen uptake ($\dot{V}_{O_2}$) at the onset of constant-load exercise has been analyzed using different mathematical models. One of the most widely accepted models is that of Henry [1], in which the time course of $\dot{V}_{O_2}$ during exercise of

moderate intensity could be well described as an exponential function. However, it is known that $\dot{V}_{O_2}$ continues to increase during heavy exercise, a phenomenon which is called $\dot{V}_{O_2}$ drift [2]. Whipp and Wasserman [3] and Linnarsson [4] demonstrated that the temporal changes in $\dot{V}_{O_2}$ during exercise in which $\dot{V}_{O_2}$ drift occurred could be expressed as the sum of two exponential components, the fast and the slow. Recently Morton [5] proposed a new model which consists of an exponential and a linear kinetics to describe the time courses of $\dot{V}_{O_2}$. Needless to say, the validity of these three models for fitting $\dot{V}_{O_2}$ kinetics should be evaluated on a physiological basis. However, experimental studies have not supported the above models sufficiently on a physiological basis [2, 6].

Arterial P_{O_2} (P_{aO_2}) and P_{CO_2} (P_{aCO_2}), lactate (LA), pH, temperature, and catecholamines were known as the controlling factors which directly or indirectly affect the exercise hyperpnea [7]. Although blood potassium concentration $[K^+]$ has been recently assumed as a direct mediator via the carotid body for the control of exercise hyperpnea [8], the exact mechanisms which determine the kinetics of $\dot{V}_{O_2}$ changes during exercise are not clearly elucidated. In the present study we examined the effects of blood gas, pH, LA, bicarbonate, and $[K^+]$ on the time courses of $\dot{V}_{O_2}$ in the steady state phase and the $\dot{V}_{O_2}$ drift phase during constant-load bicycle exercise.

Whipp [9, 10] suggested a correlation between the anaerobic threshold (AT) determined during ramp exercise and the $\dot{V}_{O_2}$ time course measured at the transition from the steady state to the $\dot{V}_{O_2}$ drift phase during step exercise. According to this hypothesis, the AT should correspond to the $\dot{V}_{O_2}$ level at the transition from steady state to the systematic increase phase (we defined this critical level in $\dot{V}_{O_2}$ as critical $\dot{V}_{O_2}$: CV_{O_2}). Therefore, we systematically examined the relationship between the CV_{O_2} and the AT detected by ventilatory gas exchange (so-called ventilatory threshold: VT) during ramp exercise.

METHODS

Eleven healthy male subjects participated in this study. The average values and their SD of age, height, weight, and maximal oxygen uptake/body weight ($\dot{V}_{O_{2max}}/bw$) of the 11 subjects were 20 ± 5.9 years, 171 ± 5.6 cm, 60 ± 5.6 kg, and 43.4 ± 9.2 ml $\cdot$ kg $^{-1} \cdot$ min $^{-1}$, respectively. Each subject was given an explanation concerning experimental procedures and risks before obtaining consent, and performed conditioning exercise prior to the test. All experiments were done in the afternoon. The temperature of the experimental room was kept between 20 and 25°C.

Experimental protocols. In order to determine the ventilatory threshold (VT), $\dot{V}_{O_{2max}}$ and the $\dot{V}_{O_2}$ time course, the subjects performed a ramp exercise and three to six constant-load exercises at different intensities for 27 min using an electro-braked bicycle ergometer on different days. The ergometer was developed in our laboratory and designed to control the torque or power regardless of

pedaling frequency [11]. The rate of increase of work intensity in the ramp exercise trial was 25 W/min following a 3 min unloaded exercise period. The intensities of the constant-load exercise were set in both cases such that the oxygen uptake ($\dot{V}_{O_2}$) would maintain a steady state or increase continuously during the exercise period. The frequency of the pedaling was maintained at 60 rpm synchronized with an electro-metronome in all experiments. Heart rate (HR), ventilation, and gas exchange were measured continuously during the whole period of exercise [12]. The measurements for ventilation and gas exchange were made every 20 s for the ramp exercise and every 30 s for the constant-load exercise.

The measurements of the chemical parameters of the blood were performed on 6 of the 11 subjects (F-K) at two intensities of constant-load exercise. Arterialized-venous blood was sampled from vv. metacarpeae dorsales or v. salvatella from the subject's hand warmed by immersion into water kept at 43°C. Blood samples were taken at rest, 1, 3, 5, 10, 15, 20, and 25 min during exercise. Blood gas, pH, bicarbonate ($[HCO_3^-]$), LA, sodium ($[Na^+]$), and potassium ($[K^+]$) concentrations were analyzed using a blood gas analyzer (Radiometer, ABL30, Denmark), LA analyzer (YSI, 23L, USA), and sodium-potassium analyzer (Radiometer, KNA2, Denmark), respectively.

Data analyses. The time courses of $\dot{V}_{O_2}$, $\dot{V}_E$, $\dot{V}_{CO_2}$, and HR from 3 min after the onset of exercise until the end of exercise, and the changes of P_{O_2} and P_{CO_2} in the arterialized venous blood ($Pa-v_{O_2}$, $Pa-v_{CO_2}$), pH, $[HCO_3^-]$, LA, $[Na^+]$, and $[K^+]$ concentrations from 3 to 25 min during constant-load exercise were fitted by linear regressions, and the correlation coefficient (r) of these variables was also calculated to examine whether these changes could maintain steady states or not.

The value of critical $\dot{V}_{O_2}$ ($C\dot{V}_{O_2}$) was determined within a range specified by values of the constants in the $\dot{V}_{O_2}$ -time regression equation, the lower limit being the maximum measured value in which the $\dot{V}_{O_2}$ time course could maintain a steady state, the upper limit being the minimum measured value in which the $\dot{V}_{O_2}$ time course began to increase significantly.

The ventilatory threshold. The ventilatory threshold (VT) was determined using the following three methods. The first method was obtained using the three linear segments model, reported by Orr *et al.* [13], for the relationship between $\dot{V}_E$ and $\dot{V}_{O_2}$. The lower intersection point of the model was determined as VT(A).

The second method (VT(B)) was to determine the breakpoint of linearity in the relationship between $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. This methodology was introduced by Beaver *et al.* [14] as the V-slope method for breath-by-breath data analysis. In this experiment the technique was applied to the data analysis obtained from the mixing chamber gas analysis. According to the protocols proposed by Beaver *et al.* [14], the data in which $\dot{V}_{O_2}$ had not yet increased significantly compared with unloaded exercise and the data from which the hyperventilation had markedly occurred were excluded from data calculation. The judgement for hyperventilation was based on the marked breakdown of linearity of the relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ (see Fig. 1A). However, in some cases the relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ seemed to

Fig. 1. Typical patterns of the relationship between minute ventilation ($\dot{V}_E$) and carbon dioxide output ($\dot{V}_{CO_2}$) during ramp exercise. Arrow indicates the break-point of linearity.

be curvilinear and therefore, this "breakdown of linearity" method could not be used to delimit the calculation range (see Fig. 1B). In these cases, data from the later stages of the exercise period were not excluded from the calculation of the $\dot{V}_{O_2}$ - $\dot{V}_{CO_2}$ relationship.

The third method (VT(C)) was to determine the $\dot{V}_{O_2}$ level where the ventilatory equivalent for $\dot{V}_{O_2}$ ($\dot{V}_E/\dot{V}_{O_2}$) reached the minimum value, so a fourth-order polynomial regression model was applied to detect the minimum point of the curve [15].

The computation of best-fit parameters for the above equations was made by the least-squares method utilizing an iterative algorithm introduced as the Simplex method [16].

Statistics. Statistical analysis were made by paired or unpaired Student's *t*-test and $p < 0.05$ was considered as significant.

RESULTS

The $\dot{V}_{O_2}$ time courses during four intensities of constant load exercise and the calculated regression lines for each condition for two subjects are shown in Fig. 2. The power outputs of the ergometer were set at 60, 75, 90, and 105 W for subject B, and 75, 90, 105, and 120 W for subject A. As shown in Fig. 2, $\dot{V}_{O_2}$ increased to a certain level within a few minutes and remained at this level during 60 and 75

Fig. 2. The time courses of oxygen uptake ($\dot{V}_{O_2}$) during different intensities of constant-load exercise for two subjects. Arrows indicate the results whether the time courses after the 3 min from the exercise onset increased significantly (↑) or not (→).

Fig. 3. The time courses of minute ventilation ($\dot{V}_E$), carbon dioxide output ($\dot{V}_{CO_2}$), and heart rate (HR) during different intensities of constant-load exercise. The intensities of exercise were the same as in Fig. 2. Arrows indicate the same as in Fig. 2.

Table 1. Comparisons of the statistical results of the time courses of $\dot{V}_{O_2}$, $\dot{V}_E$, $\dot{V}_{CO_2}$, and HR from 3 to 27 min during constant-load exercise for 11 subjects.

Subject	Exercise intensity									
	60 W	75 W	90 W	105 W	120 W	135 W	150 W	165 W	180 W	195 W
A	$\dot{V}_{O_2}$		→	↑	↑					
	$\dot{V}_E$		↓	→	↓	↑				
	$\dot{V}_{CO_2}$		↓	→	→	→				
	HR		↑	↑	↑	↑				
B	$\dot{V}_{O_2}$	→	→	↑	↑					
	$\dot{V}_E$	→	→	→	↑					
	$\dot{V}_{CO_2}$	→	→	→	↑					
	HR	↑	↑	↑	↑					
C	$\dot{V}_{O_2}$	→	→	→	↑					
	$\dot{V}_E$	→	↓	↑	↑					
	$\dot{V}_{CO_2}$	→	↓	→	→					
	HR	↑	↑	↑	↑					
D	$\dot{V}_{O_2}$	→	↑	↑						
	$\dot{V}_E$	↑	↑	↑						
	$\dot{V}_{CO_2}$	→	→	→						
	HR	↑	↑	↑						
E	$\dot{V}_{O_2}$			→				↑		
	$\dot{V}_E$			→	↑			↑		
	$\dot{V}_{CO_2}$			→	→			↑		
	HR			↑	↑			↑		
F	$\dot{V}_{O_2}$	→		→	→	↑	↑			
	$\dot{V}_E$	→		→	→	↑	↑			
	$\dot{V}_{CO_2}$	→		→	↓	→	→			
	HR	↑		↑	↑	↑	↑			
G	$\dot{V}_{O_2}$		→	↑		↑				
	$\dot{V}_E$		→	↑		↑				
	$\dot{V}_{CO_2}$		→	↑		↑				
	HR		↑	↑		↑				
H	$\dot{V}_{O_2}$			→	↑	↑				
	$\dot{V}_E$			↑	↑	↑				
	$\dot{V}_{CO_2}$			→	→	→				
	HR			↑	↑	↑				
I	$\dot{V}_{O_2}$				→		→	→	→	↑
	$\dot{V}_E$				↓		→	→	→	↑
	$\dot{V}_{CO_2}$				↓		→	→	→	↑
	HR				↑		↑	↑	↑	↑

Table 1. (continued)

Subject	Exercise intensity									
	60 W	75 W	90 W	105 W	120 W	135 W	150 W	165 W	180 W	195 W
J	$\dot{V}_{O_2}$			→	→	→	↑			
	$\dot{V}_E$			→	→	↓	↑			
	$\dot{V}_{CO_2}$			→	→	↓	→			
	HR			↑	↑	↑	↑			
K	$\dot{V}_{O_2}$		→	→	↑	↑				
	$\dot{V}_E$		→	→	→	↑				
	$\dot{V}_{CO_2}$		→	→	↓	→				
	HR		↑	↑	↑	↑				

↑, time course shows significant increase over 3 to 27 min exercise period; ↓, time course shows significant decrease over 3 to 27 min exercise period; →, time course shows no significant change over 3 to 27 min exercise period.

W-intensity exercises, but beyond these intensities $\dot{V}_{O_2}$ increased significantly over time. However, for the heaviest exercise in both subjects, the $\dot{V}_{O_2}$ time courses rose continuously for about 10 min after the onset of exercise and then leveled off. This tendency was observed in all experiments when the exercise was heavy. The slope coefficient and the constant of the regression equation increased with an increase of exercise intensity.

Figure 3 shows the time courses of changes in $\dot{V}_E$, $\dot{V}_{CO_2}$, and HR during exercise for subject B. Table 1 summarizes the changes in the slope coefficient of the regression equation of $\dot{V}_{O_2}$, $\dot{V}_E$, $\dot{V}_{CO_2}$, and HR from 3 to 27 min during exercise in each subject. HR began to rise at a lower work level (10 of 11 subjects) whereas $\dot{V}_{CO_2}$ maintained a steady state at a higher work rate compared to the changes in $\dot{V}_{O_2}$ (10 of 11 subjects). There was no significant difference between $\dot{V}_E$ and $\dot{V}_{O_2}$ time courses.

Figure 4 shows the time courses of blood gas, pH, LA, and $[K^+]$ during two intensities (90 and 120 W) of constant-load exercise in subject K. Table 2 indicates the statistical significance of the changes in these variables against time for the 12 experiments. In 7 of the 12 cases $\dot{V}_{O_2}$ maintained a steady state, and in the other 5 cases $\dot{V}_{O_2}$ increased significantly during the exercise. It was summarized from the blood measurements that:

(1) $Pa-v_{O_2}$ decreased transiently after the start of exercise, subsequently turned to increase for 5 to 10 min and then leveled off. There was no statistical significance in $Pa-v_{O_2}$ time courses from 3 to 25 min.

(2) $Pa-v_{CO_2}$ increased after the start of exercise and reached a peak at about 3 min, and after this point decreased gradually in all experiments. Most of them were statistically significant.

(3) pH decreased after the onset of exercise until about 3 min, and after this point the time courses were varied: One case decreased, two cases increased, and the

Fig. 4. The time courses of $Pa-vO_2$, $Pa-vCO_2$, blood lactate, pH, and blood potassium concentrations at two intensities of constant-load exercise for subject K.

Table 2. The statistical results of the changes in $\dot{V}O_2$, $Pa-vO_2$, $Pa-vCO_2$, pH, LA, $[Na^+]$, $[K^+]$, and $[HCO_3^-]$ time courses from 3 to 25 min during constant-load exercise in all experiments.

Subject	Intensity (W)	$\dot{V}O_2$	$Pa-vO_2$	$Pa-vCO_2$	pH	LA	$[K^+]$	$[Na^+]$	$[HCO_3^-]$
F	105	→	→	↓	→	→	→	→	→
	135	↑	→	↓	→	→	↑	→	↓
G	90	↑	→	→	↑	→	↑	→	→
	120	↑	→	↓	→	↑	↑	→	↓
H	90	→	→	↓	→	↓	→	→	↓
	120	↑	→	↓	↑	→	↑	→	↓
I	105	→	→	↓	→	→	→	→	↓
	135	→	→	↓	→	→	→	→	→
J	105	→	→	↓	→	→	→	→	↓
	135	→	→	↓	→	→	→	→	→
K	90	→	→	↓	→	→	→	→	↓
	120	↑	→	→	↓	→	↑	→	↓

↑, time course shows significant increase over 3 to 25 min exercise period; ↓, time course shows significant decrease over 3 to 25 min exercise period; →, time course shows no significant change over 3 to 25 min exercise period.

other 9 cases did not change significantly.

(4) LA increased after exercise onset, reached a peak value at 5 or 10 min and thereafter decreased gradually except in one case (subject G). The time course of LA concentration for cases in which $\dot{V}_{O_2}$ remained at steady state decreased gradually after the initial rise of 5–10 min. Moreover, for those cases in which the $\dot{V}_{O_2}$ time courses increased significantly, the LA concentration did not increase, except for one case (subject G).

(5) $[K^+]$ increased within a few minutes after the onset of exercise and reached a steady state when $\dot{V}_{O_2}$ reached the steady state. The time courses of $[K^+]$ were closely correlated with the changes of $\dot{V}_{O_2}$ time course in all experiments.

(6) $[Na^+]$ increased slightly after the start of exercise and remained at its level after 5 min, showing a steady state condition.

(7) $[HCO_3^-]$ at the first minute of the exercise increased and then decreased gradually throughout the exercise period in all experiments. Significant decreases in the time courses of $[HCO_3^-]$ after the first 3 min during exercise were found in 8 of the 12 experiments.

Figure 5 illustrates the typical patterns for the determination of VT using the three methods (A–C) for one subject. As shown in Fig. 5, mathematical analyses were applied to determine each VT. Table 3 shows the calculated values of VT by the three criteria (see METHODS). The calculated values of VT varied with criteria and, in some cases, the difference among each VT exceeded 0.5 l/min. The mean values of VT(A–C) were 1.42, 1.51, and 1.47 (l/min), and these values did not differ significantly from each other. Concerning the relationship between VT and the ranges of critical $\dot{V}_{O_2}$ ($C\dot{V}_{O_2}$), 40% of VT values were within the ranges of $C\dot{V}_{O_2}$, but 42% of VT data were lower and 18% of VT data were higher than the values of $C\dot{V}_{O_2}$. However, the mean value of the median of the range of $C\dot{V}_{O_2}$ was 1.55 l/min; this value did not differ significantly from the mean values of VT(A–C).

Fig. 5. The ventilatory threshold (VT) calculated from three criteria. The details for calculation of VT are noted in the text.

Table 3. Comparisons between the critical $\dot{V}_{O_2}$ ($C\dot{V}_{O_2}$) and the ventilatory thresholds (VTs) calculated by the three different methods (A, B, C).

Subject	$\dot{V}_{O_{2\max}}$	VT(A)	VT(B)	VT(C)	$C\dot{V}_{O_2}$ (median)
A	2.08	1.22	1.32*	1.40*	1.28 – 1.43 (1.36)
B	1.89	0.96	1.14	1.20*	1.16 – 1.27 (1.21)
C	2.02	1.03	1.59	1.23	1.40 – 1.50 (1.45)
D	2.14	1.14*	1.01*	1.10*	0.96 – 1.19 (1.07)
E	3.20	1.38*	1.80	1.31	1.33 – 1.67 (1.50)
F	2.54	1.18	1.41	1.56	1.63 – 1.72 (1.68)
G	2.65	1.72	1.52	1.69	1.19 – 1.39 (1.29)
H	2.77	1.63*	1.60*	1.59*	1.55 – 1.65 (1.60)
I	2.97	1.64	1.90	1.90	2.11 – 2.36 (2.24)
J	3.30	2.10	1.69	1.56	1.93 – 2.02 (1.98)
K	2.78	1.64*	1.67*	1.63*	1.51 – 1.81 (1.66)
Mean ($\pm$ SD)	2.58 (0.49)	1.42 (0.35)	1.51 (0.27)	1.47 (0.24)	1.46 – 1.64 (1.55) (0.34) (0.34) (0.34)

Unit: l/min in $\dot{V}_{O_2}$. * Asterisk indicates that VT is contained in the range of $C\dot{V}_{O_2}$.

DISCUSSION

$\dot{V}_{O_2}$ kinetics model for exercise. Since Henry [1] first proposed that the time courses of $\dot{V}_{O_2}$ for moderate constant-load exercise could be well fitted by the first-order exponential function, this concept has been widely accepted. However, some objections dealing with the delay time of the onset [4] and the treatment of phase 1 [17, 18] have been pointed out regarding this model. According to Henry model, $\dot{V}_{O_2}$ reaches a steady state within several minutes, since the time constant had been estimated as about 30–40 s [3, 19].

The proposed $\dot{V}_{O_2}$ kinetics models for heavy exercise have also been found insufficient. Whipp and Wasserman [3] and Linnarsson [4] proposed a bi-exponential model for $\dot{V}_{O_2}$ kinetics. Recently Morton [5] proposed a new model consisting of exponential and linear components. At present, the latter model is more simple than the bi-exponential model, and it easily detects whether the slow rise is significant or not, and whether the slow rise is linear or not. Therefore, we modified the Morton model as a linear regression model to examine the later phase of the onset response in $\dot{V}_{O_2}$ for mixing chamber data analysis. As indicated in Fig. 2, $\dot{V}_{O_2}$ time courses after the 3rd min of the exercise did not increase significantly (steady state) at lower intensity exercise, but at higher intensity, $\dot{V}_{O_2}$ turned to increase significantly as a function of time while maintaining linearity. These results suggest that $\dot{V}_{O_2}$ time courses after the initial rise could be well fitted by a linear function. However, in the heaviest work loads in Fig. 2, $\dot{V}_{O_2}$ continued to increase for 10 min and seemed to level off after this point. The phenomena that $\dot{V}_{O_2}$ leveled off at heavy constant-load exercise had not been pointed out by Morton [5], because he had examined the $\dot{V}_{O_2}$ kinetics only for short-term exercise of 8 min.

This suggests that the linear regression model is sufficiently applicable for fitting the $\dot{V}_{O_2}$ time course only after several minutes from the onset of light or moderate exercise, but is not useful for heavy exercise analysis.

Comparison between $\dot{V}_{O_2}$ time course and $\dot{V}_E$, $\dot{V}_{CO_2}$, and HR time courses. This study has revealed that the time courses of $\dot{V}_E$ and $\dot{V}_{CO_2}$ after 3 min from the onset of exercise could be well fitted by linear regressions, except for the heaviest work load, but the time courses of HR did not show any linear characteristics. The changing patterns of $\dot{V}_E$, $\dot{V}_{CO_2}$, and HR against work load did not correlate with $\dot{V}_{O_2}$. HR began to increase at lower intensity, but the increase in $\dot{V}_{CO_2}$ was delayed compared with the $\dot{V}_{O_2}$ time course. It has been observed that HR increases continuously at lower intensity exercise even when $\dot{V}_{O_2}$ maintains a steady state [20]. Broman and Wigertz [21] suggested the dissociation of the control systems between respiration and circulation during exercise. Therefore the faster response in HR may be mainly brought about by the circulatory alteration such as increased peripheral circulation [22] and/or decreased plasma volume [23].

$\dot{V}_{CO_2}$ time courses tended to decline during low-intensity exercise, and in some cases they changed significantly while $\dot{V}_{O_2}$ maintained a steady state. Consequently, significant decreases in respiratory gas exchange ratio (R) were often observed when $\dot{V}_{CO_2}$ time courses decreased significantly. These decreases in $\dot{V}_{CO_2}$ and R could be related to the changes in energy substrate utilization that are mainly due to the increased utilization of free fatty acid [24]. However, a clear difference was not found between $\dot{V}_{O_2}$ and $\dot{V}_E$ time courses in this experiment. It has already been reported that a closer relationship was observed between $\dot{V}_E$ and $\dot{V}_{CO_2}$ than between $\dot{V}_E$ and $\dot{V}_{O_2}$ [25]. In this experiment $\dot{V}_E$ time courses were found to be more closely related to those of $\dot{V}_{O_2}$ rather than $\dot{V}_{CO_2}$. The discrepancy of the results could be related to the experimental setup and protocol. Wasserman and Whipp [25] examined these relationships only during the first 6 min from the onset of exercise. Since it had been well known that the time constant of $\dot{V}_{CO_2}$ was similar to that of $\dot{V}_E$ and longer than that of $\dot{V}_{O_2}$ [19, 20], they might have been examining only the early dynamics. On the other hand, in this study we focused on the later phase of the response. So far as shown in the results, $\dot{V}_E$ is more closely related to $\dot{V}_{O_2}$ than $\dot{V}_{CO_2}$ at the later phase of the constant-load exercise. This result suggests the possibility that the systematic increase in $\dot{V}_{O_2}$ and $\dot{V}_E$ time courses after the initial dynamic phase at constant-load exercise may be controlled by a common mechanism.

Relationship between $\dot{V}_{O_2}$ time course and blood parameters. The time courses of blood gas, pH, LA, $[HCO_3^-]$, $[Na^+]$, and $[K^+]$ concentrations were examined with respect to the $\dot{V}_{O_2}$ time course in this study. Close correlation was observed only between $\dot{V}_{O_2}$ and $[K^+]$ time courses. The time courses of $Pa-v_{O_2}$, $Pa-v_{CO_2}$, pH, $[HCO_3^-]$, $[Na^+]$, and LA did not correlate with that of $\dot{V}_{O_2}$.

Casaburi *et al.* [2] suggested the contribution of blood lactate concentration, but not of body temperature and catecholamines, to the slow rise in $\dot{V}_{O_2}$ ($\dot{V}_{O_2}$ drift). On the contrary, Hagberg *et al.* [6] suggested the possibility of the influence of body temperature rise and increased ventilation on $\dot{V}_{O_2}$ drift. In the present

Fig. 6. The relationship between blood potassium concentration $[K^+]$ and oxygen uptake ($\dot{V}_{O_2}$) at rest and during two intensities of constant-load exercise for all subjects. The lowest data of each symbol indicates the resting value.

experiment the effects of body temperature and catecholamines on $\dot{V}_{O_2}$ drift were not examined, but the effect of blood lactate on the $\dot{V}_{O_2}$ drift was found to be negligible since blood lactate tended to decrease while $\dot{V}_{O_2}$ maintained a steady state. Although a close relationship between $\dot{V}_E$ and $[K^+]$ was reported [26, 27] during ramp exercise, to our knowledge we first demonstrated a close relationship between $[K^+]$ and $\dot{V}_{O_2}$ time courses at constant-load exercise.

It is well known that potassium is released from working muscles into the blood by the membrane depolarization [28] and the rise of $[K^+]$ is closely related to the intensity of exercise [29, 30]. Furthermore, the time constant of the $[K^+]$ response was reported as about 35 s for heavy exercise [30] and 44 s for submaximal exercise [31]. These figures of the time constant of $[K^+]$ are thought to be correlated with the time constant of $\dot{V}_{O_2}$ reported previously [19, 20], suggesting a linear relationship between $\dot{V}_{O_2}$ and $[K^+]$. Therefore the relationship between $\dot{V}_{O_2}$ and $[K^+]$ during exercise was reexamined in the present study. The relationship between $\dot{V}_{O_2}$ and $[K^+]$ obtained at rest and during two intensities of constant-load exercise has clearly demonstrated that close linear relationship ($r > 0.9$) does exist between $\dot{V}_{O_2}$ and $[K^+]$ in all subjects (Fig. 6). This suggests that $[K^+]$ may play an important role in affecting the $\dot{V}_{O_2}$ time courses for constant-load exercise. However, at present we have no direct evidence that $[K^+]$ controls the $\dot{V}_{O_2}$ in the same way as it controls $\dot{V}_E$ [8]. We have examined the relationship between $\dot{V}_{O_2}$ and $[K^+]$ only for submaximal exercise but not for maximal exercise in the present

study. Further experiments will be needed to solve this problem.

Relationship between VT and critical $\dot{V}_{O_2}$. The concept of anaerobic threshold (AT) was first introduced by Wasserman *et al.* [32] as the point at which metabolic acidosis caused by LA production (lactate threshold: LT) and concomitant changes in ventilatory gas exchange (ventilatory threshold: VT) began to occur during incremental or ramp exercise. Despite numerous studies, controversy still remains on the best method to determine AT. The main issues for detection of AT are whether LT is equal to VT [33, 34] and which is the best criterion for detection of VT [15]. We focused on the relationship between VT and $C\dot{V}_{O_2}$ in the present study, because Whipp [9, 10] has already suggested the correlation between AT and the $\dot{V}_{O_2}$ time courses from steady state phase to the $\dot{V}_{O_2}$ drift phase. VTs were determined by three mathematical analyses reported previously [13–15] and compared with $C\dot{V}_{O_2}$. Although the calculated values of VT varied with different methods of measurement, the variations were not significant. The mean value of the median of $C\dot{V}_{O_2}$ did not differ significantly from the mean of VT(A–C). However, 60% of all the measured VTs were not found in the ranges of $C\dot{V}_{O_2}$. Therefore we concluded that it is impossible to confirm that VT is equal to $C\dot{V}_{O_2}$ from the statistical analysis. Another approach to confirm the relationship between VT(AT) and $C\dot{V}_{O_2}$ is to assess the control mechanisms of these two parameters. According to Whipp's hypothesis, blood lactate does not increase from the resting level and $\dot{V}_{O_2}$ maintains a steady state after the initial dynamic phase during constant-load exercise at an intensity below AT. However, it is also known that LA is produced in muscles at the onset of constant-load exercise due to restriction of the oxygen supply. The initial rise in blood LA after the onset of exercise is most probably due to the anaerobic metabolism of this phase. Orak *et al.* [35] reported that the time courses of blood lactate during low-intensity constant-load exercise (40% of $\dot{V}_{O_{2max}}$) did not differ significantly from that at resting level. But they found that LA after the onset of exercise of moderate intensity (60% of $\dot{V}_{O_{2max}}$), reached a peak and then decreased gradually. The time courses of LA in the present experiment resembles those of LA at the intensity of 60% $\dot{V}_{O_{2max}}$ in Orak's study. In addition, the median of $C\dot{V}_{O_2}$ corresponded to 60% (47–72%) of the individual's $\dot{V}_{O_{2max}}$ in this study. Therefore, it is assumed that the intensity at which blood LA does not increase from resting level is lower than the intensity that we have measured, and does not correspond to $C\dot{V}_{O_2}$. The disagreement in the time courses between LA and $\dot{V}_{O_2}$ has also been suggested by Oyono-Enguelle *et al.* [36]. Based on this evidence, it is suggested that blood LA is not directly correlated with the systematic increase in $\dot{V}_{O_2}$ during constant-load exercise. This indicates that the underlying physiological mechanism of AT determined during incremental or ramp exercise and that of the $\dot{V}_{O_2}$ drift during constant-load exercise are different.

In conclusion, the time courses of $\dot{V}_{O_2}$ after the initial dynamic phase during constant-load exercise were well correlated with those of $[K^+]$, but were not correlated with those of blood LA, pH, or blood gas. It is suggested that $[K^+]$ may play an important role in controlling the $\dot{V}_{O_2}$ kinetics. The values of critical $\dot{V}_{O_2}$ that

were defined as the level at which $\dot{V}_{O_2}$ drift began to occur at constant-load exercise were not always in agreement with the ventilatory threshold (VT). Therefore, it is still unclear whether it can be stated with certainty that VT is equal to $C\dot{V}_{O_2}$.

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