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The Relationship between Arterial Plasma Potassium Concentration and Ventilation during Exercise in Patients with Chronic Obstructive Pulmonary Disease

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Summary. **This study aims to elucidate the relationship between arterial plasma potassium concentration ($[K^+]_a$) and ventilation, and evaluate the effect of hyperoxia on the ventilation-$[K^+]_a$ relationship during incremental exercise testing in patients with chronic obstructive pulmonary disease (COPD).**

We studied 16 male patients with COPD. Using a bicycle ergometer, each patient started to exercise with a work load of 25W, which was increased in steps of 5W in one minute intervals until the symptom-limited end-point. The same trial with oxygen inhalation was also performed in 6 out of 16 patients.

During the exercise testing in room air ($n=16$), $[K^+]_a$ increased from the baseline (3.82 ± 0.18 mEq/L) to 4.62 ± 0.33 mEq/L ($p<0.01$). Once exercise stopped, $[K^+]_a$ decreased rapidly. In all patients, the increase in minute ventilation volume($\dot{V}_E$) was significantly correlated with the elavation of $[K^+]_a$ ($p<0.05$). Ventilatory response to $[K^+]_a$ (the slope of $\triangle\dot{V}_E/\triangle K^+$) varied markedly among the patients (13.1 to 50.7 L/min/mEq/L), and was correlated with forced vital capacity (FVC)($P<0.05$). During the trial with oxygen inhalation ($n=6$), the mean slope of $\triangle\dot{V}_E/\triangle K^+$ was not depressed, compared with the room air run, which was 21.9 ± 11.9 in the former and 25.4 ± 13.1 L/min/mEq/L in the latter, respectively.

These findings indicate that: 1) ventilation and $[K^+]_a$ were correlated during exercise; 2) the slope of ventilatory response to $[K^+]_a$ differed markedly among the patients, and was correlated with FVC; and 3) hyperoxia did not significantly affect the ventilation-$[K^+]_a$ relationship. We conclude that, while $[K^+]_a$ may play some role, certain unknown factors may also be involved in determining the degree of exercise hyperpnea in patients with COPD.

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INTRODUCTION

Recent studies on breathing control suggest that the arterial plasma potassium concentration ($[K^+]_a$) is important for the development of exercise hyperpnea[1-4]. In anesthetized cats, an increase in arterial potassium by 3.9 ± 0.5 mEq/L caused an increase in ventilation of approximately 25% (253 ± 22 ml/min), and this effect was abolished peripherally by chemodenervation. This report suggests that the infusion of KCL stimulates carotid bodies and increases ventilation[5]. This excitatory effect of $[K^+]_a$ is enhanced by hypoxia and reduced or abolished by hyperoxia[6,7]. Potassium-stimulated ventilation in spontaneously breathing decerebrated cats is eliminated by hyperoxia[8].

In normal human subjects, $[K^+]_a$ is correlated with ventilation during exercise[9-11]. Patients with chronic obstructive pulmonary disease (COPD) tend to develop hypoxia during exercise, and it is conceivable that ventilatory responses to $[K^+]_a$ may be enhanced in patients with COPD. Yoshida et al. showed that ventilation and $[K^+]_a$ were correlated during exercise in COPD patients, but contrary to expectations, the augmented ventilation in response to elevated $[K^+]_a$ was smaller in these patients than in normal young subjects[12]. The ventilation-$[K^+]_a$ relationship in COPD patients thus needs to be elucidated further. We investigated the relationship between $[K^+]_a$ and ventilation during an incremental

exercise testing. We also studied the effect of hyperoxia on the ventilation-$[K^+]_a$ relationship in these COPD patients.

METHODS

Patients

Sixteen male patients with COPD according to American Thoracic Society (ATS) criteria[13] participated in the study. Informed consents were obtained from all patients. The physical characteristics of the patients are shown in Table 1.

Table 1. Characteristics of the patients

Number of patients		16
Age	(yrs)	63.8±10.4
%VC	(%)	91.9±21.0
FEV1	(L)	1.07± 0.51
FEV1% (T)	(%)	37.1±14.2
%TLC	(%)	113.3±17.1
%RV	(%)	158.7±43.5
RV/TLC	(%)	51.0± 8.4
%DLCO	(%)	70.4±18.4
pH		7.42± 0.03
PaO_2	(mmHg)	78.1±10.7
$PaCO_2$	(mmHg)	41.1± 7.2

Values are mean±SD

Exercise testing in room air

Patients exercised on a bicycle ergometer while breathing room air through a mouthpiece with a nose clip. Exercise was initiated at a work load of 25 W, which was increased in steps of 5 W in one minute intervals until the symptom-limited endpoint. Arterial O_2 saturation was measured with a pulse oximeter, of which a sensor was placed to the finger tip (OLV1200, NIHON KOHDEN). Expired gas was collected every minute for measurements of respiratory rate (f) and tidal volume (V_T). Minute ventilation volume ($\dot{V}_E$) was then calculated (CHEST RS-1100H). To obtain the arterial blood samples, a teflon catheter was inserted into the radial artery. During the incremental exercise test, arterial blood samples were withdrawn every 3 min to measure $[K^+]_a$, pH, PaO_2 $PaCO_2$, and $[HCO3^-]$. During the recovery period, arterial blood samples were taken every 2 min. The plasma potassium concentration was measured with a flame photometry. Arterial pH, PaO_2, and $PaCO_2$ were measured with blood gas analyzer (ABL3, Radiometer, Copenhagen). $[HCO3^-]$ was calculated by the Henderson-Hasselbalch equation.

Exercise testing with oxygen inhalation

Six of the 16 patients exercised with the same protocol under oxygen inhalation. Oxygen administration was performed to keep their arterial O_2 saturation more than 98%.

Statistical analysis

Values are presented as mean±SD. Linear regression analysis was determined by a least-squares method. Comparison of differences among the parameters was made by ANOVA, and differences between oxygen and room air trials were assessed by the paired t-test. Statistical significance was accepted at $P<0.05$.

RESULTS

Exercise testing in room air

Fig. 1 shows changes in ventilatory parameters and $[K^+]_a$ in a representative patient (Case 4). Time courses of $\dot{V}_E$, f, V_T and $[K^+]_a$ were similar; however, V_T reached a plateau level well before maximum exercise. $\dot{V}_E$, f and V_T were significantly correlated with $[K^+]_a$ (Fig. 2).

Table 2 shows the correlations between $\dot{V}_E$, f, V_T and $[K^+]_a$ in room air for all patients. The increase in $\dot{V}_E$ was significantly correlated with the elevation of $[K^+]_a$ in all patients ($p<0.05$). The slope: $\triangle\dot{V}_E/\triangle K^+$, varied markedly among the patients (13.1 to 50.7 L/min/mEq/L). Respiratory rate (f) was also significantly correlated with $[K^+]_a$ in all patients, but tidal volume (V_T) was correlated significantly in only eight of the 16 patients.

The changes in $[K^+]_a$, $\dot{V}_E$ and arterial blood gases at rest, maximum exercise, and in the recovery period are shown in Table 3. $[K^+]_a$ increased significantly from the baseline (3.82±0.18 mEq/L) to 4.62±0.33 mEq/L ($p<0.01$). The PaO_2 level during exercise decreased significantly from the resting level (78.1± 10.7 mmHg) to 61.9±11.8 mmHg during maximal exercise.

The slope of $\triangle\dot{V}_E\triangle K^+$ was not correlated with resting PaO_2 $\triangle PaO_2$ (magnitude of PaO_2 depression from resting to maximal exercise, the amount of exercise desaturation) or the lowest PaO_2 during

exercise, but was correlated with the forced vital capacity (FVC)($p<0.05$).

Exercise Testig both in room air and with oxygen inhalation

The slope of $\triangle \dot{V}_E \triangle K^+$ did not significantly differ between room air and oxygen breathing in six patients (25.4 ± 13.1 in the former and 21.9 ± 11.9 L/min/mEq/L in the latter, respectively)(Fig. 3). Table 4 shows the changes in $[K^+]_a$, $\dot{V}_E$, and arterial blood gases at rest, maximum exercise, and in the recovery period in six patients who repeated the two trials. There were no differences between $[K^+]_a$ and $\dot{V}_E$ at maximum exercise conducted with and without oxygen inhalation.

DISCUSSION

In normal subjects, minute ventilation ($\dot{V}_E$) has shown to be correlated with $[K^+]_a$ during exercise[9,10,11]. Similar results have been reported in patients with COPD [12,14]. In the present study, we also observed a correlation between $[K^+]_a$ and $\dot{V}_E$. We have further examined the relationship between additional breathing parameters and $[K^+]_a$ (Table 2). $\dot{V}_E$ and f were correlated with $[K^+]_a$. Both increased progressively with increased work loads, but V_T culminated far below the maximum exercise.

Yoshida et al. reported that the slope of $\triangle \dot{V}_E/\triangle K^+$ was significantly lower in patients with COPD than in normal young subjects[12]. In our study, the slope of $\triangle \dot{V}_E/\triangle K^+$ varied markedly among patients. We examined the factors possibly affecting the slope of $\triangle \dot{V}_E/\triangle K^+$. The excitatory effect of hyperkalemia on ventilation is reported to be enhanced by hypoxia, and reduced or abolished by hyperoxia[6,7,8,15]. Patients with COPD tended to develop hypoxia during exercise; therefore, the ventilatory response to potassium was expected to be enhanced in patients with COPD. In the present study, the PaO_2 showed a significant decrease during exercise (Table 3). Although we speculated that the slope of $\triangle \dot{V}_E/\triangle K^+$ would be augmented by advancing the degree of hypoxia, it was not correlated with PaO_2 at rest, $\triangle PaO_2$ or the lowest PaO_2 duing exercise. The slope of $\triangle \dot{V}_E/\triangle K^+$ was significantly correlated only with forced vital capacity (FVC). These results suggest that the variation in the $\triangle \dot{V}_E/\triangle K+$ slope may have resulted from additional, unknown factors or from the impaired respiratory function, rather than advancing hypoxia. It has been reported that hyperoxia

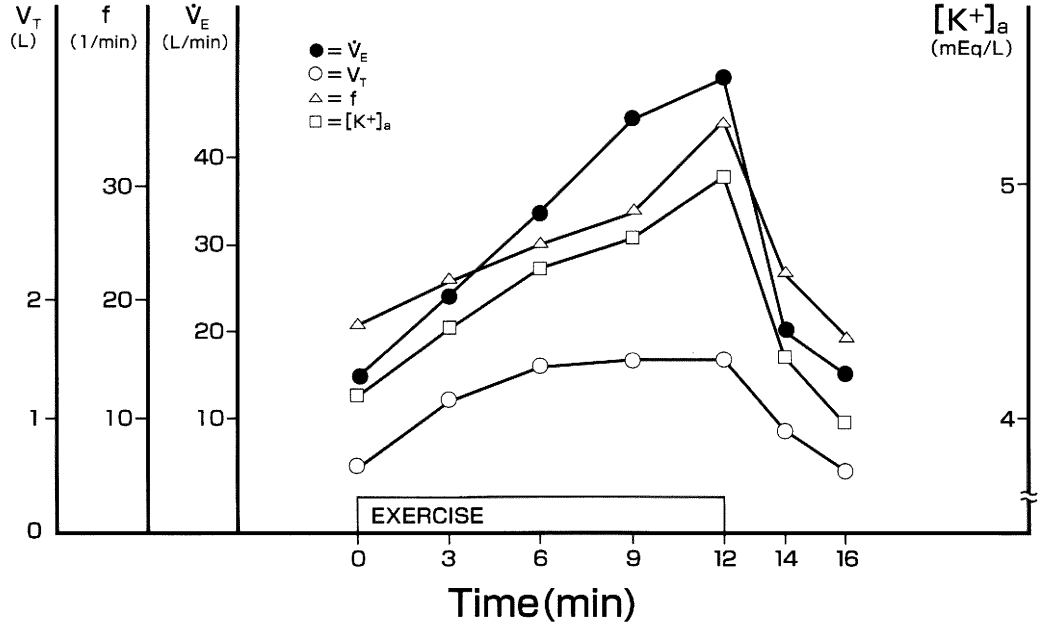

Fig. 1 Changes in ventilation and $[K^+]_a$ during rest, exercise, and the recovery phase in case 4. ● = $\dot{V}_E$; ○ = V_T; △ = f; □ = $[K^+]_a$. The profiles of the time courses in $[K^+]_a$, $\dot{V}_E$ and f were similar to each other. However, that of V_T was slightly different, as V_T seemed to have reached a ceiling level long before the end of exercise.

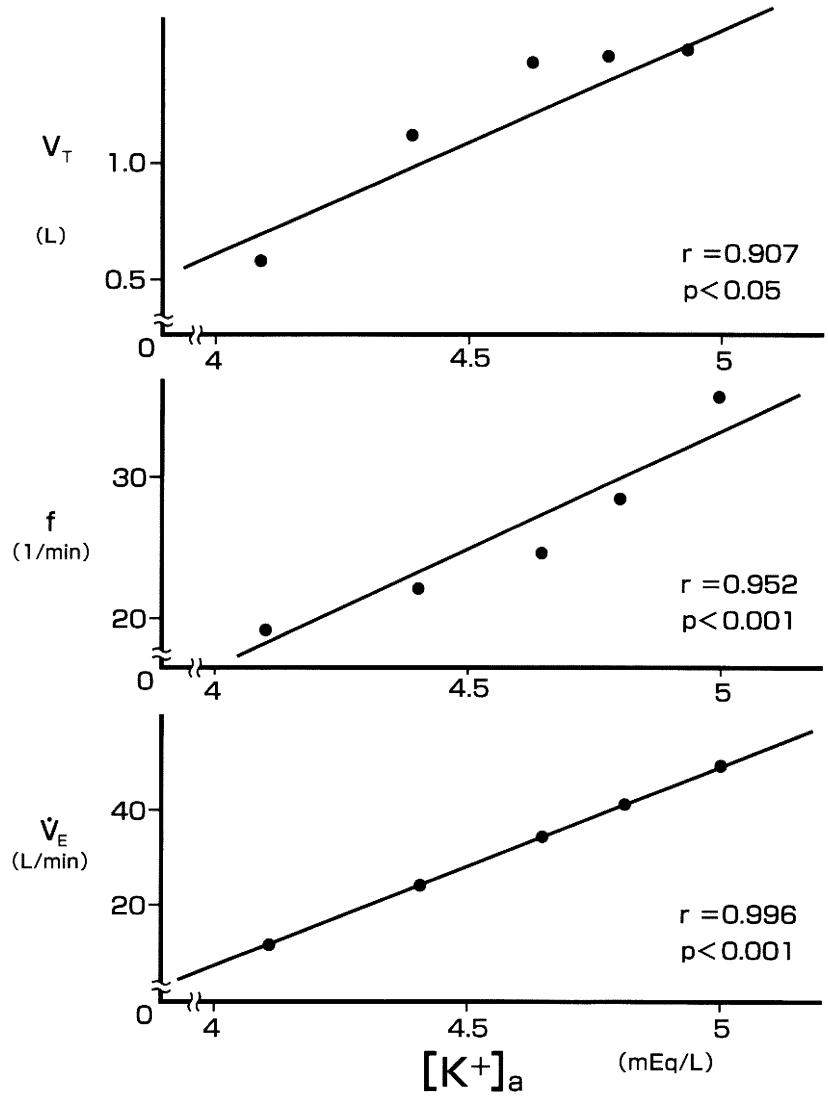

Fig. 2 Relationship between $[K^+]_a$ and ventilation during exercise in case 4. There was a siginificant linear correlation between $[K^+]_a$ and $\dot{V}_E$, V_T, and f.

reduces the ventilatory response to potassium[8]. However, the mean slope of $\triangle\dot{V}_E/\triangle K^+$ was not depressed in our six patients (Fig. 3) who exercised with oxygen inhalation, indicating that hyperoxia did not significantly affect the $\triangle\dot{V}_E/\triangle K^+$ relationship. We paid particular attention to four patients who exhibited more than 10 mmHg PaO_2 depression during exercise breathing room air. In these patients, the slope of $\triangle\dot{V}_E/\triangle K^+$ was effectively depressed with oxygen inhalation. The ventilatory response to potassium may be reduced by hyperoxia in patients with severe hypoxia during exercise. Although these findings provide slight support for the hypothesis that hyperoxia mitigates the ventilatory response to potassium in COPD patients, the overall mean slope of $\triangle\dot{V}_E/\triangle K^+$ was not statistically affected in all six patients who exercised with oxygen inhalation. This may imply that $\triangle\dot{V}_E/\triangle K^+$ slope is not only exclusively determined by the degree of hypoxia but also other unsolved factors. Further studies are needed to clarify this problem.

In conclusion, we showed that ventilation and $[K^+]_a$ were correlated during exercise in patients with COPD, and that the slope of $\triangle\dot{V}_E/\triangle K^+$ varied markedly among patients, being correlated with forced vital capacity (FVC). Hyperoxia did not sig-

Table 2. Correlation coefficients between the serum potassium and ventilatory parameters and their slopes

	$\triangle\dot{V}_E/\triangle K^+$		$\triangle f/\triangle K^+$		$\triangle V_T/\triangle K^+$	
No.	(L/min/mEq/L)	r	(f/min/mEq/L)	r	(L/mEq/L)	r
1	25.1	0.89*	13.0	0.93*	0.49	0.79
2	42.7	0.99##	30.5	0.97#	0.42	0.75
3	35.7	0.95*	9.0	0.91*	1.08	0.94**
4	40.1	0.99**	16.7	0.95##	0.90	0.91*
5	33.5	0.99##	14.5	0.99#	0.71	0.95*
6	13.1	0.88**	7.6	0.83*	1.07	0.74
7	29.3	0.98##	11.4	0.97#	0.87	0.95**
8	25.5	0.94*	11.2	0.99*	0.41	0.68
9	23.6	0.95**	23.8	0.98#	0.24	0.88*
10	32.2	0.98##	16.1	0.96#	0.70	0.89**
11	50.7	0.87#	22.1	0.86#	1.24	0.70*
12	19.3	0.91*	14.4	0.95#	0.35	0.66
13	18.3	0.77*	3.8	0.70*	0.74	0.73*
14	28.2	0.85##	17.1	0.84*	0.37	0.42
15	15.9	0.84*	8.7	0.72*	0.34	0.65
16	20.2	0.76##	15.8	0.71##	0.19	0.47
mean	28.3		14.7		0.57	
±SD	±10.4		±6.6		±0.33	

* $p<0.05$, ** $p<0.02$, # $p<0.01$, ## $p<0.001$.

Table 3. Changes in $[K^+]_a$, $\dot{V}_E$ and arterial blood gases (N=16)

		Resting	Maximum exercise	Recovery
$[K^+]_a$	(mEq/L)	3.82±0.18	4.62±0.33#	3.87±0.25
$\dot{V}_E$	(L/min)	11.9±1.65	37.4±9.8#	19.5±4.5
PaO_2	(mmHg)	78.1±10.7	61.9±11.8#	85.8±13.7
$PaCO_2$	(mmHg)	41.1±7.2	44.3±6.9#	40.8±6.2
pH		7.42±0.03	7.34±0.05#	7.35±0.05#
$[HCO_3^-]$	(mEq/L)	25.4±2.9	22.9±2.8#	21.2±3.1#

Exercise endurance time (min) 9.13±2.96

#; $p<0.01$: vs resting Values are mean±SD.

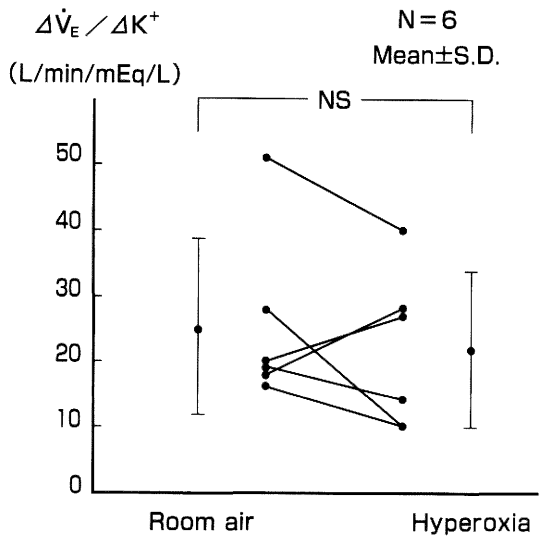

Fig. 3 The slope of $\triangle \dot{V}_E/\triangle K^+$ was not depressed by hyperoxia, compared to that in breathing room air. The mean $\triangle \dot{V}_E/\triangle K^+$ slopes of No.11 to 16 patients were 21.9±11.9 and 25.4±13.1 L/min/mEq/L in oxygen and room air inhalation, respectively.

Table 4. Changes in $[K^+]_a$, $\dot{V}_E$ and arterial blood gases under room air and oxygen inhalation (N=6)

		Resting	Maximum exercise	Recovery
$[K^+]_a$	(mEq/L)			
	room air	3.78±0.17	4.32±0.23	3.77±0.27
	oxygen	3.84±0.13	4.52±0.15	3.91±0.34
$\dot{V}_E$	(L/min)			
	room air	11.3±1.7	29.5±4.6	20.0±3.7
	oxygen	11.1±2.8	28.8±7.9	21.8±5.2
PaO_2	(mmHg)			
	room air	77.2±15.8	57.7±12.9	83.4±22.9
	oxygen	184.2±54.4**	194.1±85.9*	227.4±68.5**
$PaCO_2$	(mmHg)			
	room air	38.8±11.0	45.2±11.3	40.6±11.7
	oxygen	40.3±9.93	50.0±10.6	42.3±11.0
pH				
	room air	7.43±0.04	7.33±0.03	7.36±0.04
	oxygen	7.42±0.04	7.31±0.03*	7.34±0.04
$[HCO_3^-]$	(mEq/L)			
	room air	25.4±4.6	24.4±4.5	22.4±4.4
	oxygen	26.0±4.5	24.4±4.8	22.2±4.5
Exercise endurance time	(min)			
	room air		6.67±3.01	
	oxygen		9.50±3.39**	

** ; $p<0.01$, * ; $p<0.05$ vs room air Values are mean±SD.

nificantly affect the relationship between ventilation and $[K^+]_a$, but the slope of $\triangle \dot{V}_E/\triangle K^+$ was depressed with oxygen inhalation in patients who exhibited severe exercise desaturation. Further studies are required to assess the effect of hyperoxia on the relationship between ventilation and $[K^+]_a$ during exercise.

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