Relationship between Maximal Pulmonary Ventilation and Arterialized Venous Blood Potassium and Dopamine Concentrations Obtained at Exhaustion in Man

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Abstract: This study was performed to test the hypothesis that potassium concentration in arterialized blood may be closely related to maximal pulmonary ventilation ($\dot{V}E_{max}$) obtained at exhaustion during maximal exercise in man. Eleven healthy men performed bicycle exercise with incremental loading at 60 rpm until exhaustion. Pulmonary ventilation ($\dot{V}E$), oxygen uptake ($\dot{VO}_2$), and heart rate (HR) were determined continuously throughout the experiment. Arterialized venous blood samples were collected to measure potassium ([K$^+$]), lactate ([La]), hydrogen ion (pH), catecholamine ([CA]), and dopamine ([DA]) concentrations. A significant correlation ($r=0.98-0.88$) between $\dot{V}E$ and [K$^+$], [La], and pH during exercise was observed in all subjects. Furthermore, a close relationship was found in this study between dopamine concentration measured at exhaustion ([DA]$_0$) and maximal pulmonary ventilation per kilogram of body weight ($\dot{V}E_{max}/W$) ($r=-0.668$, $p<0.05$) or maximum oxygen uptake per kilogram of body weight ($\dot{VO}_{2max}/W$) ($r=0.720$, $p<0.05$). However, no significant correlation was found between $\dot{V}E_{max}/W$ and $[K^+]_0$ ($r=0.202$, NS), $[La]_0$ ($r=-0.096$, NS), and pH$_0$ ($r=0.344$, NS). These results suggest that dopamine may play a more important role in the determination of maximal pulmonary ventilation during exercise in man than K$^+$ or pH. [Japanese Journal of Physiology, 48, 17–23, 1998]

Key words: maximal pulmonary ventilation, bicycle exercise, dopamine, potassium, lactate.

Maximum oxygen uptake ($\dot{VO}_{2max}$) as an index of aerobic work capacity in humans is considered to be limited by several factors such as pulmonary ventilation, lung perfusion and diffusion, cardiac output, peripheral perfusion and diffusion, and mitochondrial oxygen utilization [1]. Among these factors, it is well known that pulmonary ventilation increases with increasing workload, and maximal pulmonary ventilation ($\dot{V}E_{max}$), which is generally obtained at exhaustion during a maximal exercise test for several minutes, is closely associated with $\dot{VO}_{2max}$ for each subject.

It has hitherto been reported that pulmonary ventilation ($\dot{V}E$) during exercise is regulated by a combination of neural and humoral drives. Humoral control of ventilation during exercise is mediated by arterial chemoreceptors, which can be stimulated by increased hydrogen ion (or decreased hydrogen ion) (pH), increased carbon dioxide partial pressure ($PCO_2$), catecholamine (CA), and potassium (K$^+$) [2], and inhibited by an increase in dopamine (DA) [3]. With regard to potassium, Band et al. [4] have observed similarity of the time courses of arterial potassium and ventilation changes during bicycle ergometer exercise. Linton and Band [5] suggest that potassium released from working muscles may be an important drive to ventilation in exercise because of an increase in carotid chemoreceptor activity, which closely follows the arterial potassium concentration. A further increase in ventilation when intravenous injections of potassium chloride were given to anesthetized

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cats produced a rise in arterial plasma potassium within the range of those occurring in man during exercise. In fact, the rise in $K^+$ is directly proportional to the increase in $\dot{V}E$ during exercise in normal subjects [6, 7]. This correlation is also seen during incremental exercise in patients with McArdle’s syndrome [8, 9]. From these results, it is possible to assume that $\dot{V}E_{\text{max}}$ would be higher in those subjects with higher $K^+$, but not hydrogen ion.

In the previous study [10], we found a significant correlation between $\dot{V}E_{\text{max}}$ and venous blood potassium concentration ([K$^+$]v), but not lactate concentration ([La]v). However, it should be stressed here that in the previous study the measurement period was different for $\dot{V}E_{\text{max}}$ and [K$^+$]v, [K$^+$]v, and [La]v, were determined at 1 min ([K$^+$]v) after maximal exercise, and $\dot{V}E_{\text{max}}$ was obtained at exhaustion. Furthermore, arterial blood potassium concentration declined rapidly within about 3 min after maximal exercise and was a little lower than venous blood potassium [11, 12]. Thus it seems necessary to reexamine the relationship between $\dot{V}E_{\text{max}}$ and arterial blood potassium concentration, which are obtained simultaneously at exhaustion.

On the other hand, DA is a prominent amine in the carotid body, and exogenously administered dopamine is known to inhibit ventilation or carotid sinus nerve discharge in cats [13-15] and humans [16, 17]. One exception to this is in the dog, where high doses of exogenous dopamine stimulate the carotid body followed briefly by an inhibition [18]. More physiological doses of dopamine, however, are inhibitory to the carotid body and ventilation in the dog [19]. It has been observed that the rate of release of DA by the carotid body is increased by hypoxia [3], and DA content of the carotid body in rats increased after chronic hypoxia [20]. Moreover, a very tight linear relationship was found between the decrease of extracellular pH and the release of DA or the carotid sinus nerve (CSN) discharge [21]. There was a similar relationship in vivo between blood pH and CSN action potential frequency [22]. Because it is well known that blood oxygen partial pressure ($PO_2$) and pH decrease gradually with increasing workload during maximal exercise in human subjects, DA concentration seems to be increased at exhaustion even if the subject reaches exhaustion within about 10–15 min. Although to our knowledge no data are available concerning dopamine in exhausting exercise, arterial blood dopamine concentration may closely correlate with $\dot{V}E_{\text{max}}$ in a human subject.

The main purpose of this study, therefore, is to confirm whether arterialized venous blood potassium ([K$^+$]v) and dopamine ([DA]v) concentrations obtained at exhaustion of incremental maximal exercise are significantly associated with $\dot{V}E_{\text{max}}$ in normal subjects. The relationships between $\dot{V}E_{\text{max}}$ and blood lactate ([La]v), hydrogen ion (pHv), and catecholamine ([CA]v) concentrations obtained at exhaustion were also examined.

**METHODS**

Eleven healthy male subjects participated in this study. Five belonged to the track and field club of our university and trained mainly by running for about 2 h a day with a frequency of 3 times a week. All subjects received detailed explanations concerning the experimental nature and risks of the study before consent was obtained. The average values and their standard deviations of age, weight, and height were 25.5±6.6 years, 64.7±6.6 kg, and 172.4±5.1 cm. The study was approved by the Human Research Committee of the Research Center of Health, Physical Fitness and Sports of Nagoya University.

The subjects came to the laboratory at least twice. On the first day, all subjects were familiarized with the equipment and procedures involved in the study. Furthermore, vital capacity (VC), forced vital capacity (FEV$_{1.0}$), and maximum voluntary volume (MVV) of each subject were measured by means of a spirometer (Benedict type). On the second day, which was a few days after the first day, maximal bicycle exercise was performed on each subject. Maximal exercise tests were always done in the afternoon 2 h after the subjects had eaten. A respiratory mask and electrodes were attached to each subject’s face and chest to continuously determine pulmonary ventilation ($\dot{V}$E), oxygen uptake ($\dot{V}$O$_2$), carbon dioxide output ($\dot{V}$CO$_2$), and heart rate (HR) during rest, exercise, and recovery.

Forster et al. [23] have reported that arterialization with a temperature of about 43°C on the skin allows for a valid estimation of arterial PCO$_2$ and pH. Furthermore, according to McLoughlin et al. [24], arterialized venous values of pH, PCO$_2$, lactate, K$^+$, and epinephrine were the same as arterial values without serious error. To collect arterialized venous blood samples, a needle was inserted into superficial veins (v. metacarpeae dorsales or v. salvatella) of the dorsum of the left hand. Then the hand was covered with a vinyl sack to prevent it from contacting water, and the sack was warmed by immersion in water kept at 43°C throughout the experiments [25]. After the subject rested in a sitting position on the bicycle ergometer for 10 min, maximal exhaustive exercise was carried out on the bicycle ergometer at 60 rpm with incremen-
Maximal Pulmonary Ventilation and Dopamine

tal loading. The frequency of pedaling was maintained at 60 rpm synchronized with a metronome during exhaustive exercise. The incremental workload was set so that the subjects could drive for about 11–15 min before they were exhausted, i.e., workload was increased each 2 min by 180 kgm·min⁻¹ (29.4 W) until 10 or 12 min from the start of exercise, and it was then increased each 2 min by 90 kgm·min⁻¹ (14.7 W) until exhaustion. Subjects performed exhaustive exercise in which their right hand gripped the bicycle’s handle and their left hand was inserted into the warm water of a plastic water tank, as shown in Fig. 1. They were also given strong verbal encouragement to maintain frequency and work rate for as long as possible. The subjects rested in the same sitting position for 3 min after the exhaustive exercise.

Pulmonary minute ventilation (VE) was measured by pneumotachograph (Westrom, WLCU-5201, Japan) attached to the respiratory face mask. The pneumotachograph was calibrated by means of a 1-l calibration pump before experiments. Expired gas (5 l) was passed through the mixing chamber via a connecting tube, and sample gas was then drawn from the mixing chamber to analyze O₂ and CO₂ concentrations in the expired gas. The concentration of O₂ and CO₂ in the expired gas was determined by a gas analyzer (Minato Ikagaku, MG-360, Japan), which was calibrated with calibration gases. The electrocardiogram was also recording continuously throughout the whole period of experiments. All signals were converted from analog to digital by A-D converter (Canopus, ADX-98-E) and analyzed by computer (NEC, PC-9801VX, Japan). The measurement of VE, VO₂, VC₀₂, and HR were made every 30 s for the incremental-load exercise. Arterialized venous blood samples (about 5 ml) were drawn into heparinized syringes through an 18G Teflon catheter at rest during exercise and recovery. During exercise, arterialized blood was collected at 1.5, 3.5, 5.5, 7.5, and 9.5 min, and thereafter at about 1-min intervals until exhaustion. Blood samples were also taken at exhaustion, 1 min, and 3 min during the recovery period. Blood hydrogen ion (pH), sodium ([Na⁺]), potassium ([K⁺]), and lactate ([La⁻]) concentrations were analyzed by using a blood gas analyzer (Radiometer, ABL30, Denmark), a sodium-potassium analyzer (Radiometer, KNA2, Denmark), and the enzymatic technique. Dopamine ([DA]) and catecholamine ([CA]) concentrations were analyzed only for the samples obtained at rest and exhaustion by means of the high-performance liquid chromatography (HPLC) method.

Statistical analysis was made by a paired Student’s t-test, and p<0.05 was considered significant.

RESULTS

The changes over time for heart rate (HR), minute ventilation (VE), oxygen uptake (VO₂), arterialized venous blood hydrogen ion (pH), potassium ([K⁺]), and lactate ([La⁻]) concentrations are shown in Fig. 2. HR, VE, VO₂, [K⁺] and [La⁻] all increased with increasing workload until exhaustion, pH being the exception. Average values (±SD) of maximal heart rate (HRₘₐₓ), maximum ventilation (VEₘₐₓ), maximum oxygen uptake (VO₂ₘₐₓ), and maximum oxygen uptake per kilogram of body weight (VO₂ₘₐₓ/W) were 184.5±
Table 1. Chemical parameters of arterialized blood samples at rest and exhaustion.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exhaustion</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>7.391±0.008</td>
<td>7.281±0.016**</td>
</tr>
<tr>
<td>La (mmol·l⁻¹)</td>
<td>0.80±0.06</td>
<td>8.10±0.60**</td>
</tr>
<tr>
<td>[Na⁺] (mmol·l⁻¹)</td>
<td>140±0.84</td>
<td>145±1.23**</td>
</tr>
<tr>
<td>[K⁺] (mmol·l⁻¹)</td>
<td>4.00±0.07</td>
<td>5.85±0.07**</td>
</tr>
<tr>
<td>AD (pg·ml⁻¹)</td>
<td>99.3±11.5</td>
<td>884±183**</td>
</tr>
<tr>
<td>NA (pg·ml⁻¹)</td>
<td>540±79</td>
<td>3,789±210**</td>
</tr>
<tr>
<td>DA (pg·ml⁻¹)</td>
<td>16.6±2.2</td>
<td>37.3±4.3**</td>
</tr>
</tbody>
</table>

Values are mean and ±SE. Statistical difference between rest and exhaustion, **p<0.01.

![Graph](image)

Fig. 3. Relationship between pulmonary ventilation (VE) and potassium ([K⁺]), lactate ([La]) concentration, or pH during maximal exercise in the subject T.T.

![Graph](image)

Fig. 4. Relationship between maximal pulmonary ventilation per kilogram of body weight (VE_{max}/W) and arterialized plasma potassium concentration ([K⁺]₀), plasma blood lactate concentration ([La]₀) and hydrogen ion (pH₀) obtained at exhaustion.

![Graph](image)

Fig. 5. Relationship between maximal pulmonary ventilation per kilogram of body weight (VE_{max}/W) and plasma dopamine concentration ([DA]₀) obtained at exhaustion.

12.0 beats·min⁻¹, 124.4±12.8 l·min⁻¹, 3.36±0.23 l·min⁻¹, 48.9±3.4 ml·kg⁻¹·min⁻¹, respectively.

The arterialized venous blood pH, [La], [Na⁺], [K⁺], adrenaline ([AD]), nor-adrenaline ([NA]), and dopamine ([DA]) obtained at rest and exhaustion are shown in Table 1. Although pH decreased gradually until exhaustion, the values for [La], [Na⁺], [K⁺], [AD], [NA], and [DA] at exhaustion were significantly (p<0.01) higher than at rest.

Figure 3 indicates the relationship between VE and [K⁺], [La], and pH during incremental bicycle exercise in the given subject (T.T.). Pulmonary ventilation was closely correlated (r=0.979–0.993, p<0.01) with arterialized venous blood potassium, lactate, and hydrogen ion as shown in Fig. 3. These results were almost the same in all subjects. Figure 4 shows the relationship between maximal pulmonary ventilation per kilogram of body weight (VE_{max}/W) and arterialized blood potassium concentration ([K⁺]₀), lactate concentration ([La]₀), and hydrogen ion (pH₀) determined at exhaustion. The VE_{max}/W was not significantly correlated with [K⁺]₀ (r=0.202), [La]₀ (r=−0.096) and pH₀ (r=0.344). However, the dopamine concentration measured at exhaustion ([DA]₀) correlated linearly and inversely with VE_{max}/W (r=−0.668, p<0.05) as shown in Fig. 5. Furthermore, there was also a significant linear correlation between [DA]₀ and maximum oxygen uptake per kilogram of body weight (VO_{2max}/W) (r=0.720, p<0.05).

**DISCUSSION**

The main result of this study was that maximal pulmonary ventilation per kilogram of body weight was inversely correlated (r=−0.668, p<0.05) with arterialized venous blood dopamine concentration measured at exhaustion, but not with potassium, lactate,
and hydrogen ion concentrations.

It has hitherto been reported that stimulation of arterial chemoreceptors by hydrogen ion is thought to be responsible for the ventilatory drive during heavy exercise [26]. However, Hagberg et al. [8] and Paterson et al. [9] have observed the close relationship between pulmonary ventilation and arterial potassium concentration not only in normal subjects, but also in McArdle's patients. They suggest that hyperventilation accompanying high-intensity exhaustive exercise may be the result of hyperkalemia mediated through a carotid body other than lactic acidosis or lung CO₂ flux. Busse et al. [27] also support the idea that the potassium increase may contribute to the ventilatory drive, especially during heavy exercise. As shown in Fig. 3, a close relationship between [K⁺]a and V̇E during exercise supports the role of this potassium ion as a potent stimulus of exercise ventilation. Paterson et al. [6] have observed that the time course of [K⁺]a at the end of hard exercise is much closer to that of V̇E than the time course of [H⁺], is. These results suggest that maximal pulmonary ventilation may be closely associated with blood potassium concentration in humans.

It was found in the previous study that V̇E_{max} was significantly correlated (r=0.750, p<0.05) to potassium concentration in the venous blood measured at 1 min ([K⁺]a_{1.0}) after maximal exhaustive exercise in healthy subjects [10]. As described previously, however, plasma potassium concentration raised during exercise declines immediately at a rapid rate within 3 min following the cessation of exercise. Arterial plasma potassium concentration ([K⁺]a) at exhaustion is slightly lower (about 0.15 mmol·l⁻¹) than that of venous plasma [K⁺]a, [11, 12]. Furthermore, the arterial venous concentration difference reversed immediately after the termination of exercise [28, 29]. Thus the present study was conducted to confirm the relationship between V̇E_{max} and arterialized venous blood potassium concentration measured at exhaustion.

Busse and Maassen [30] predicted that the real difference between plasma [K⁺] in arterial blood and arterialized blood of the superficial forearm veins would be distinctly less than 0.1 mmol·l⁻¹. McLoughlin et al. [24] also showed that accurate estimates of arterial values of pH, PCO₂, and K⁺ could be made from the arterialized venous results during incremental testing. As shown in Fig. 4, it was found in this study that no significant relationship exists between maximal pulmonary ventilation per kilogram of body weight (V̇E_{max}/W) and arterIALIZED venous blood potassium concentration ([K⁺]a) or lactate concentration ([La]a) obtained at exhaustion. At present we cannot explain the discrepancy of results found in the previous and present studies based on a physiological grounds, though it might be mainly due to the difference in the blood sampling time and blood composition, i.e., arterialized and venous blood. Furthermore, McLoughlin et al. [31] suggested that the combined respiratory stimulant effect of elevation of [K⁺]a and acute lactic acidosis is more than additive. It is possible to assume that there is individual variation in the interaction between potassium and hydrogen ion and in the chemosensitivity of the carotid body to potassium even if the hydrogen ion obtained at exhaustion is the same, since it is well known that chemosensitivity of hypercapnia and/or hypoxia are much different in healthy subjects [32]. However, it is necessary to confirm this assumption.

It has been recently reported that with increasing exercise intensity, the rise in V̇E becomes increasingly greater than the rise in plasma [K⁺] [33]. Casaburi et al. [34] have undertaken to test the hypothesis that V̇E changes in direct proportion to changes in arterial potassium concentration ([K⁺]a) during moderate exercise. They suggest that the dissimilar dynamics of [K⁺]a and V̇E seem inconsistent with a major role for [K⁺]a as a proportional controller of ventilation during nonsteady state moderate exercise in man, since they found V̇E amplitude and phase were not highly correlated with [K⁺]a, during sinusoidal work rate variation. Although we cannot rule out a role for [K⁺]a in the hyperpnea of heavy exercise [31], these results suggest that the plasma [K⁺]a may not be the sole determinant of maximal pulmonary ventilatory regulation during exhaustive exercise in man.

The ventilation during exercise is mediated by arterial chemoreceptors and is stimulated not only by an increased potassium, hydrogen ion, and PCO₂, but also by catecholamines [35]. In this study no significant relationships were found between V̇E_{max}/W and pH (r=0.344, NS), adrenaline (r=0.159, NS) and noradrenaline (r=0.059, NS) determined at the exhaustion. It is of interest, however, that V̇E_{max}/W is inversely correlated (r=−0.668, p<0.05) with dopamine concentration as shown in Fig. 5. Exogenously applied DA has been reported do more than simply inhibit the carotid sinus nerve (CSN), also that DA antagonists do more than increase CSN discharge or ventilation [3]. For example, Wach et al. [36] studied the effect on ventilation of the dopamine D₂ antagonist domperidone and observed augmentation of ventilation during hypoxia in control rats and in chronically hypoxic rats. Because domperidone does not cross the blood brain barrier, it can have no central effect. Interestingly, Bee and Pallot [37] have
found that in chronically hypoxic rats, acute hypoxic ventilatory response was greater as chronic exposure to hypoxia was shorter, in which the ventilatory responses were inversely related to carotid body dopamine content. Moreover, this supports the view that acidic stimuli activate the synthesis of CA and the release of DA [3]. It is well known that arterial blood saturation (SaO₂) and pH decrease greatly during heavy exercise in highly trained endurance athletes [38, 39]. Although no available data are available concerning dopamine secretion-synthesis balance during exercise, it is possible to speculate that dopamine content in the carotid body could increase in subjects who exhibit exercise-induced hypoxemia and acidemia. Because the subject who participated in this study was not well trained with respect to maximum oxygen uptake (45.4–56.1 ml·kg⁻¹·min⁻¹), exercise-induced hypoxemia would seemingly not be brought about by exertion. There are no significant correlations between [DA]₀ and [pH]₀, or [La]₀. Furthermore, it is also possible to assume that dopamine concentration may be related to exhaustion time, since catecholamine concentration increases with increasing workload-through the sympathetic-adrenal medullary system during exhaustive exercise in man. However, no significant relationship was noted between exhaustion time and [DA]₀ or [CA]₀, even though the subjects exhausted within 10–15 min in this experiment. Thus on physiological grounds we cannot explain the reasons of increment in the dopamine concentration or the individual differences observed here.

On the other hand, maximum pulmonary ventilation (VE max) estimated during maximal exercise is generally higher in the trained subject than in the untrained subject, even though the maximum voluntary volume (MVV) in both the trained and untrained subjects is about the same [40]. Higher VE max in the trained group is considered to be due to increment of strength and/or endurance of respiratory muscle. Respiratory muscle is considered to consume much more oxygen during exhaustive exercise to ensure high VE max in the trained subject, indicating the energy-stealing from the working muscle as suggested by Bye et al. [41]. In other words, it is possible to speculate that dopamine may play a role of depressing the energy-stealing by respiratory muscle or overwork of respiratory muscle, especially in well-trained athletes. Therefore exercise-induced hypoxemia could be due to the depression of VE max by DA. However, this speculation needs further investigation.

In conclusion, the present study indicates that maximal pulmonary ventilation and maximum oxygen uptake per kilogram of body weight were significantly correlated with dopamine concentration measured at exhaustion of maximal bicycle exercise, but not with potassium, lactate, and hydrogen ion concentrations. These results suggest that dopamine content may contribute significantly to the limitation of maximal pulmonary ventilation during maximal exhaustive exercise in man.

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Maximal Pulmonary Ventilation and Dopamine

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23