Exercise-induced Rise in Arterial Potassium is Enhanced in Patients with Impaired Exercise Tolerance

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SUMMARY

We assessed the changes in arterial potassium concentration during exercise and recovery in relation to exercise tolerance in patients with impaired exercise tolerance. Sixteen patients with cardiac disease were subjected to a cardiopulmonary exercise test on a cycle ergometer. Arterial potassium and lactate concentrations were measured every minute during and after exercise, and ventilatory threshold (VT) and lactate threshold (LT) were identified. Before exercise, arterial potassium concentration was $3.8 \pm 0.3 \text{ mEq/l}$. It increased to $4.1 \pm 0.3 \text{ mEq/l}$ at LT ($p < 0.002$ versus at rest), to $4.2 \pm 0.3 \text{ mEq/l}$ at VT, and to $4.8 \pm 0.5 \text{ mEq/l}$ at peak exercise ($p < 0.001$ versus at LT, $p < 0.001$ versus at VT). At an exercise intensity equivalent to 30, 40, 50 or 60% of predicted maximum oxygen uptake, the increase in arterial potassium showed a negative and significant correlation with %LT ($r = -0.62 \sim -0.72$, $p < 0.01 \sim 0.05$) and %VT ($r = -0.62 \sim -0.75$, $p < 0.001 \sim 0.05$), where %LT and %VT represent the ratios of LT and VT to the predicted maximum oxygen uptake, respectively. There was a good correlation between the rate of fall in potassium concentration during recovery and its increase during exercise. It was concluded that in patients with impaired exercise tolerance, the greater the degree of exercise intolerance, the greater the increase in arterial potassium concentration during exercise, and the steeper the fall in potassium concentration during recovery. Because the rise in potassium concentration during exercise and its fall during recovery were greater when the exercise level exceeded the anaerobic threshold, exercise levels below the anaerobic threshold are recommended for patients with cardiac diseases. (Jpn Heart J 35: 37–48, 1994)

Key words: exercise intolerance cardiopulmonary exercise testing lactate threshold ventilatory threshold anaerobic threshold

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SINCE Fenn’s excellent review article in 1936,1) there have been numerous well-documented reports linking physiological exercise to a transient increase in serum potassium concentration. The origin of that increased serum potassium has been proven to be the exercising muscles.2,3) In healthy subjects, the release of potassium is reported to be proportional to the workload,4) and serum potassium concentration does not rise significantly until the lactate threshold is surpassed.5) After exercise, serum potassium concentration falls rapidly to levels equal to, or below, rest values due to active uptake of potassium.6,7) Both the increase in potassium during exercise and hypokalemia after exercise increase the incidence and severity of arrhythmias in patients with heart disease.8) However, changes in potassium concentration during exercise and recovery in patients with impaired exercise tolerance have not previously been reported.

The relationship between the degree of exercise intolerance and the degree of exercise-induced increase in serum potassium also remains unknown. Because exercise-induced hyperkalemia can be reduced by physical training in animals9) as well as in healthy volunteers,10) it is possible that exercise intolerance is accompanied by pronounced hyperkalemia during exercise.

The objective of this study was to assess the changes in arterial potassium concentration during exercise and recovery in relation to exercise intensity and exercise tolerance in patients with impaired exercise tolerance. This is the first study on exercise-induced potassium change in a group of patients with exercise intolerance. To ensure accuracy when evaluating exercise tolerance, we used both the lactate threshold (LT) and the ventilatory threshold (VT) as indices of exercise tolerance.

**Subjects and Methods**

**Subjects:** The study population consisted of 16 patients, all male, aged 57 ± 12 (mean ± SD) years. The mean value of VT was 13.0 ± 2.5 ml/kg/min (range: 8.3 to 17.7). This level of exercise tolerance is equivalent to New York Heart Association cardiac functional class II or III.11) The clinical diagnosis was old myocardial infarction in 4 patients, vasospastic angina pectoris in 3, effort angina pectoris in 2, chest pain syndrome without known cardiac disease in 2, valvular heart disease in 2, and other cardiac diseases (myocarditis, congenital heart disease or syndrome of X) in 3 patients. In patients with old myocardial infarction or myocarditis, the left ventricular ejection fraction measured by left ventriculography or first-pass radionuclide angiography was <50% (39 ± 11%, mean ± SD). Exercise intolerance in these patients and in those with valvular heart disease or congenital heart disease was thought to be due, at least in part, to cardiac dysfunction. In the other patients, the left ventricular ejection
fraction at rest was normal (72 ± 11%, mean ± SD). Exercise intolerance in these patients was assumed to be due in part to physical deconditioning, because none of them had a respiratory or hematological disorder, and all were leading a very sedentary lifestyle.

None of the subjects had renal disorders or were under treatment with diuretics or beta-adrenoceptor blockers. Three patients were under treatment with calcium antagonists, 2 were taking oral nitrates and 6 were taking both. Medical treatment was not suspended during the study. All patients were well informed of the nature of this study and agreed to participate in it.

**Cardiopulmonary exercise testing:** The subjects exercised on an upright cycle ergometer (Lode model Corival 400, Netherlands). After a 5-minute rest period on the ergometer, the exercise test was begun with a 3-minute warm-up at an unloaded exercise level, followed by an initial load of 20W, which was increased at a rate of 10W per minute until the target heart rate (85% of predicted maximal heart rate\(^{29}\)) was obtained, or until they were limited by leg fatigue. None of the subjects stopped exercising due to anginal pain. Heart rate and 1 electrocardiogram (ECG) lead were continuously monitored throughout the test. Cuff blood pressure was measured with an automatic indirect manometer and the 12-lead ECG was recorded every minute. Respiratory gas analysis was performed continuously throughout the test using an Oxycon-4 (Mijnhardt model Ox-4, Netherlands). Each patient had a brachial artery cannula placed before exercise for arterial blood sampling.

**Measurement of respiratory gas exchange and determination of VT:** Oxygen uptake (VO\(_2\)), carbon dioxide output (VCO\(_2\)) and minute ventilation (VE) were measured every 30 seconds during the test. The gas analysis system was carefully calibrated before each patient was studied. The results of the respiratory gas analysis were plotted graphically, and VT was identified by inspection as the value of VO\(_2\) at which the beginning of a systematic increase in the ventilatory equivalent for oxygen (VE/VO\(_2\)) occurred without an increase in the ventilatory equivalent for carbon dioxide (VE/VCO\(_2\))\(^{13}\).

**Arterial blood sampling, measurement and determination of LT:** Using a 3-way stopcock, arterial blood samples for potassium and lactate determination were drawn at baseline, every minute during exercise, and at 1, 2, 3, 4, 5, 7 and 10 minutes after the end of exercise. To avoid hemolysis, particular care was taken in the collection of blood. Arterial blood was allowed to fill syringes under arterial pressure. All samples were taken in identical fashion by the same investigator. The potassium concentration was determined by flame photometry as soon as feasible (within 1 hour of sampling). To measure lactate, the blood sample was immediately precipitated with iced perchlorate solution and centrifuged to obtain a clear supernatant for analysis. The lactate concentration was determined
using an enzymatic technique. In 7 patients, blood samples were also collected in iced tubes with EDTA-2Na at baseline, at the time of VT and at peak exercise, to measure epinephrine and norepinephrine by high performance liquid chromatography.

In 3 patients, the microhematocrit was determined in triplicate immediately upon collection of blood samples to determine whether the measured rise in plasma potassium concentration also indicated an augmentation of the total content of plasma potassium. If there is no loss nor gain of the plasma potassium during exercise, the expected potassium concentration \( (C_{OE}) \) is calculated according to the formula given by van Beaumont et al\(^6\) as follows:

\[
C_{OE} = \frac{H_{tpost}(100 - H_{tpre})}{H_{tpre}(100 - H_{tpost})} \times C_{Opre}
\]

where \( C_{Opre} \) is the baseline potassium concentration, and \( H_{tpre} \) and \( H_{tpost} \) are the baseline hematocrit and that during exercise, respectively. The actual increase in the total content of plasma potassium is then the difference between the expected \( (C_{OE}) \) and measured \( (C_{OM}) \) concentrations.

LT was determined as the value of \( VO_2 \) at which an abrupt increase in lactate concentration was noted.

Data analysis: To take into consideration individual differences regarding age, body weight and height of the patients when evaluating exercise tolerance and exercise intensity, \( \%VT \), \( \%LT \) and \( \%VO_2_{max} \), which represent the ratios of VT, LT, and \( VO_2 \) to the predicted \( VO_2_{max} \),\(^{14}\) were calculated. We defined the “sub-peak” exercise level as a midpoint between the level of LT and peak exercise to examine the changes in plasma potassium during exercise in detail. All values are expressed as mean ± standard deviation. Comparisons between levels were analyzed for statistical significance using the paired t-test. We considered a \( p < 0.05 \) level as significantly different.

**Results**

Hemodynamics and ECG: The peak workload of 16 patients was 107 ± 17W. The heart rate increased from 80 ± 8/min at rest to 134 ± 13/min \( (p < 0.002) \) at the peak exercise level, the systolic blood pressure from 128±16mmHg to 184 ± 18mmHg \( (p < 0.002) \), and the diastolic blood pressure from 80 ± 9mmHg to 100 ± 17mmHg \( (p < 0.002) \). Exercise ECGs were positive (defined as a horizontal or downsloping ST segment depression of ≥0.1mV measured 0.08 seconds after the J point) in 2 patients.

Respiratory gas exchange and exercise tolerance: The peak \( VO_2 \) was
20.2 ± 3.9 ml/kg/min with a range of 11.8 to 26.8, and the peak %VO\textsubscript{2max} was 69 ± 15% with a range of 46 to 95. LT was 11.2 ± 3.1 ml/kg/min (range from 7.6 to 15.7) and %LT was 39 ± 10% (range from 25 to 63). The value of VT was significantly higher than that of LT (p < 0.02) and was 13.0 ± 2.6 ml/kg/min (range 8.3 to 17.7), and %VT was 45 ± 9% (range 33 to 68). The sub-peak VO\textsubscript{2} corresponded to 15.7 ± 3.2 ml/kg/min (range 10.3 to 20.9) and 54 ± 12% (range 38 to 79) of predicted VO\textsubscript{2max}.

**Arterial potassium (Figure 1):** At rest, the arterial potassium concentration was within the normal range in all patients (3.8 ± 0.3 mEq/l, range 3.2 to 4.3). During exercise, it increased significantly to 4.1 ± 0.3 mEq/l (range 3.6 to 4.6) at LT (p < 0.002 versus at rest), to 4.2 ± 0.3 mEq/l (range 3.6 to 4.7) at VT (p < 0.02 versus at LT), to 4.4 ± 0.3 mEq/l (range 3.7 to 4.9) at sub-peak (p < 0.002 versus at VT) and to 4.8 ± 0.5 mEq/l (range 3.9 to 6.2) at peak exercise (p < 0.001 versus at LT, p < 0.001 versus at VT, p < 0.002 versus at sub-peak). Whereas the rate of potassium rise as related to increasing VO\textsubscript{2} below LT and VT was calculated as 0.012 mEq/l/%VO\textsubscript{2max} and 0.013 mEq/l/%VO\textsubscript{2max} respectively, that above VT was as much as 0.025 mEq/l/%VO\textsubscript{2max}. This indicates that exercise above VT resulted in a rise in the potassium concentration twice as steep as that seen for exercise below VT. While the rise in arterial potassium concentration from baseline values to those at LT and VT was 0.3 ± 0.1 mEq/l (range 0.2 to 0.5) and 0.4 ± 0.1 mEq/l (range 0.2 to 0.6), respectively, the rise from baseline

**Figure 1.** Changes in arterial potassium concentration (mean±SD) during and after exercise. K = potassium concentration; LT = lactate threshold; VT = ventilatory threshold; %VO\textsubscript{2max} = ratio of oxygen uptake to predicted maximum value; *: p < 0.02; **: p < 0.002.
Figure 2. Relationship between the increase in potassium during exercise and the fall in potassium during recovery. Increase in K during exercise = potassium concentration at peak exercise minus potassium concentration at baseline; fall in K during recovery = potassium concentration at peak exercise minus potassium concentration at the nadir in the recovery period.

Table I. Mean Values for Expected and Measured Potassium Concentrations Before and During Exercise

<table>
<thead>
<tr>
<th></th>
<th>COE</th>
<th>COM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>4.0 ± 0.1</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>VT</td>
<td>4.1 ± 0.1</td>
<td>4.3 ± 1.0</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>4.3 ± 0.1</td>
<td>4.9 ± 0.2*</td>
</tr>
</tbody>
</table>

COE = expected potassium concentration calculated with hematocrit change according to the formulae given by van Beaumont et al; COM = measured potassium concentration; *significantly different from COE (p < 0.05).

Table II. Correlations between Exercise Tolerance and the Increase in Arterial Potassium Concentration

<table>
<thead>
<tr>
<th>Index of exercise tolerance</th>
<th>Increase in arterial potassium concentration at exercise intensity of x% of VO(2_{\text{max}})</th>
<th>Correlation coefficient</th>
<th>(\rho) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%LT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>-0.72</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>-0.62</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>-0.68</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>-0.65</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>%VT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>-0.62</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>-0.66</td>
<td>&lt; 0.01</td>
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<td>50</td>
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</tr>
<tr>
<td>60</td>
<td>-0.62</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

%LT = VO\(_2\) at lactate threshold/predicted VO\(_2\)\(_{\text{max}}\); %VT = VO\(_2\) at ventilatory threshold/predicted VO\(_2\)\(_{\text{max}}\).
values to those at peak exercise was as much as $0.9 \pm 0.4$ mEq/l (range 0.6 to 1.9). During recovery, the arterial potassium concentration decreased rapidly to $4.1 \pm 0.3$ mEq/l ($p < 0.002$ versus at peak exercise) within 1 minute after exercise, reaching a nadir between the 2nd and 4th minutes after exercise ($3.8 \pm 0.2$ mEq/l). The arterial potassium concentration at nadir did not differ significantly from that at baseline. The fall in the potassium concentration during the first 2 to 4 minutes of recovery (potassium concentration at peak exercise minus potassium concentration at nadir) correlated well with the increase in potassium during exercise (potassium concentration at peak exercise minus potassium concentration before exercise) ($y = 0.89x + 0.19$, $p < 0.002$, $r = 0.87$, Figure 2).

On the basis of the increment in hematocrit in 3 patients (from $39.3 \pm 2.0\%$ at baseline to $40.9 \pm 2.6\%$ at peak exercise; $p = 0.06$), the measured potassium concentration at peak exercise was significantly higher than the potassium concentration expected by hematocrit change ($4.9 \pm 0.2$ mEq/l versus $4.3 \pm 0.1$ mEq/l, $p < 0.05$, Table 1).

**Relationship between the increase in arterial potassium during exercise and the exercise tolerance:** At an exercise intensity equivalent to 30, 40, 50 or 60% of predicted VO$_{2\text{max}}$, the increase in arterial potassium (potassium concentration at each exercise intensity minus potassium concentration at baseline) showed a negative and significant correlation with %LT ($r = -0.62 \sim -0.72$,

![Figure 3](image-url)

**Figure 3.** Relation between the %LT and the increase in potassium concentration at an exercise intensity of 50% of predicted maximum oxygen uptake. %LT = ratio of lactate threshold to predicted maximum oxygen uptake; K = potassium concentration.
Figure 4. Relation between the %VT and the increase in potassium concentration at an exercise intensity of 50% of predicted maximum oxygen uptake. %VT = ratio of ventilatory threshold to predicted maximum oxygen uptake; K = potassium concentration.

$p < 0.01 \sim 0.05$, Table II). The same kind of correlation was also observed between the increase in arterial potassium at each exercise intensity and %VT ($r = -0.62 \sim -0.75$, $p < 0.001 \sim 0.05$, Table II). Figures 3 and 4 show the relations between the %LT and %VT with the increase in arterial potassium at the exercise intensity of 50% of VO$_2$max.

**Catecholamines:** The concentration of arterial epinephrine was not elevated significantly during exercise (0.13 ± 0.07 ng/ml at baseline, 0.13 ± 0.07 ng/ml at VT, 0.16 ± 0.09 ng/ml at peak exercise), however, a significant increase in norepinephrine was observed (from 0.32 ± 0.10 ng/ml at baseline to 0.58 ± 0.27 ng/ml at VT ($p < 0.02$), and to 0.85 ± 0.37 ng/ml at peak exercise ($p < 0.02$ versus at baseline)). No correlation was observed between the increase in arterial potassium and the levels of catecholamines either at VT or at peak exercise.

**DISCUSSION**

This is the first study on exercise-induced potassium changes in patients with exercise intolerance. In these patients, exercise above the anaerobic threshold (VT or LT) induced a rate of rise in potassium concentration twice that observed during exercise below the anaerobic threshold. However, the exercise intensity at the anaerobic threshold was also accompanied by a significant increase in arterial potassium concentration. In the recovery period, the level of
arterial potassium decreased rapidly to baseline levels within 2 to 4 minutes in all patients, showing a good correlation with its increase during exercise. On the other hand, the elevation in potassium concentration showed a negative and significant correlation with the indices of exercise tolerance, that is, VO$_2$ at LT/predicted VO$_{2\text{max}}$ and VO$_2$ at VT/predicted VO$_{2\text{max}}$ at exercise intensities of 30, 40, 50 and 60% of predicted VO$_{2\text{max}}$. These data indicate that the greater the degree of exercise intolerance, the greater the rise in arterial potassium concentration, and the steeper the fall in potassium concentration during recovery.

During short, intensive muscular activity, fluid is lost from the vascular compartment. However, this hemoconcentration occurs without change in red cell mass, therefore changes in intravascular total potassium content can be assessed from changes in hematocrit. In our study, the measured potassium concentration was significantly higher than the concentration expected based on hematocrit changes. This result indicates that the exercise was accompanied by an augmentation of total plasma potassium content. This observation is in agreement with the findings of van Beaumont et al.5

The origin of increased plasma potassium during exercise is the working muscles. While this study was not designed to address the mechanisms involved in the increase in potassium during exercise in patients with impaired exercise tolerance, we may reasonably interpret our data as follows.

The release of potassium is in part a consequence of muscle cell depolarization. Incomplete re-uptake of potassium by sodium, potassium-adenosinetriphosphatase (Na,K-ATPase) may account for the rise in extracellular potassium after each repolarization of the action potential. Knochel et al reported that, in dogs, moderate training reduced the rise in venous potassium during exercise; at the same time an increase of 165% in the activity of Na,K-ATPase prepared from muscle homogenates was detected. Kjeldsen et al also observed that the activity of Na,K-ATPase in rats, measured as total concentration of $^3$H-ouabain binding sites, increased by 46% after intensive swim training and decreased upon deconditioning. Therefore, it is possible that exercise intolerance is accompanied by a decrease in the number of Na,K-ATPase units in the skeletal muscle, which would lead to a reduced re-uptake of potassium.

On the other hand, Kjeldsen et al reported that in humans, exercise-induced hyperkalemia can be reduced by moderate training without any change in skeletal muscle Na,K-ATPase. Therefore, it is also possible that the greater increase in arterial potassium in patients with exercise intolerance could be a consequence of a decreased activation of Na, K-ATPase in skeletal muscle.

Furthermore, many studies have suggested that ATP-sensitive potassium channels may also play an important role in the release of potassium during heavy exercise. Since a reduction in intracellular pH in the presence of ATP
enhances ATP-sensitive potassium channel activity,\textsuperscript{21}) changes in pH may be important in coupling cellular metabolism to this channel activity. Thus, an early decrease in cellular pH in patients with impaired exercise tolerance possibly leads to an increased release of potassium during exercise.

Catecholamines released from the adrenal medulla as well as sympathetic nerve endings are of importance in the control of potassium concentration. Catecholamines are known to increase Na\textsubscript{+},K\textsubscript{+}-ATPase-mediated potassium uptake in skeletal muscle,\textsuperscript{22}) via beta\textsuperscript{2}-adrenoceptor stimulation\textsuperscript{23}); beta\textsuperscript{2}-adrenoceptor stimulation induces hypokalemia.\textsuperscript{24}) Inversely, alpha-adrenoceptor stimulation inhibits potassium uptake by skeletal muscle,\textsuperscript{25}) and raises the plasma potassium concentration.\textsuperscript{26}) In the present study, although a significant increase in circulating norepinephrine was observed, the increase in potassium concentration did not correlate with the norepinephrine concentration. Stimulation of Na\textsubscript{+},K\textsubscript{+}-ATPase by increased catecholamine may play an important role in the rapid decrease in arterial potassium concentration during recovery,\textsuperscript{22,23}) however, it may be only partly responsible for the increase in potassium during exercise.\textsuperscript{26})

Our data are in line with the conclusions of Coplan et al\textsuperscript{27}) who found that exercise above the anaerobic threshold resulted in a significantly larger increase in venous potassium concentration compared with exercise below the anaerobic threshold in healthy men. This finding indicates that anaerobic metabolism in exercising skeletal muscle is associated with a larger potassium release than aerobic metabolism is. This might be because lactic acid production due to anaerobic metabolism decreases the intracellular pH which in turn inhibits membrane Na\textsubscript{+},K\textsubscript{+}-ATPase,\textsuperscript{26}) and enhances ATP-sensitive potassium channel activity,\textsuperscript{21}) leading to an increased loss of cellular potassium.

In conclusion, in this study, we have demonstrated that for patients with impaired exercise tolerance, the greater the degree of exercise intolerance, the greater the rise in arterial potassium concentration, and the steeper the fall in potassium concentration during recovery. Moreover, the rise in arterial potassium concentration was greater with exercise above the anaerobic threshold. These findings are of critical importance in understanding the underlying characteristics of exercise intolerance. To prevent the hazardous effects of hyperkalemia during exercise and of hypokalemia during recovery in patients with cardiac disease and exercise intolerance, we recommend exercise of an intensity that does not exceed the anaerobic threshold for rehabilitation and for daily activity.

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