Potassium dynamics are attenuated in hyperkalemia and a determinant of QT adaptation in exercising hemodialysis patients

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Potassium dynamics are attenuated in hyperkalemia and a determinant of QT adaptation in exercising hemodialysis patients. J Appl Physiol 115: 498–504, 2013. First published May 30, 2013; doi:10.1152/japplphysiol.01019.2012.—Disturbances in plasma potassium concentration (pK) are well known risk factors for the development of cardiac arrhythmia. The aims of the present study were to evaluate the effect of hemodialysis on exercise pK dynamics and QT hysteresis, and whether QT hysteresis is associated with the pK decrease following exercise. Twenty-two end-stage renal disease patients exercised on a cycle ergometer with incremental work load before and after hemodialysis. ECG was recorded and pK was measured during exercise and recovery. During exercise, pK increased from 5.1 ± 0.2 to 6.1 ± 0.2 mEq/L (mean ± SE; P < 0.0001) before hemodialysis and from 3.8 ± 0.1 to 5.1 ± 0.1 mEq/L (P < 0.0001) after hemodialysis. After 2 min of recovery, pK had decreased to 5.0 ± 0.2 mEq/L and 4.1 ± 0.1 mEq/L (P < 0.0001) before and after hemodialysis, respectively. pK increase during exercise was accentuated after hemodialysis. The pK increase was negatively linearly correlated with pK before exercise (β = −0.21, R2 = 0.23, P = 0.001). QT hysteresis was negatively linearly correlated with the decrease in pK during recovery (β = −28 ms/mEq/L, R2 = 0.36, P = 0.006). Thus, during recovery, low pK was associated with relatively longer QT interval. In conclusion, new major findings are an accentuated increase in pK during exercise after hemodialysis, an attenuated increase in pK in hyperkalemia, and an association between pK and QT interval adaptation during recovery. The acute pK shift after exercise may modulate QT interval adaptation and trigger cardiac arrhythmias.

potassium; Na-K-ATPase; cardiac repolarisation; QT adaptation; exercise; end-stage renal disease; hemodialysis

DISTURBANCES IN PLASMA POTASSIUM CONCENTRATION (pK) are well known risk factors for the development of cardiac arrhythmia. Thus both hyperkalemia and hypokalemia are associated with cardiac arrhythmia and sudden cardiac death (14). This is mainly related to the influence of potassium (K) on the membrane potential, excitability, and action potential duration in cardiac cells. In addition to being a constituent of the K gradient, the extracellular K concentration modulates sodium-potassium-adenosinetriphosphatase (Na-K-ATPase) activity and the potassium currents I\(_{K1}\) and I\(_{Kr}\) (13, 38).

During physical exercise, skeletal muscle loses K secondary to the outward K current during the muscle action potential (30). Since skeletal muscles constitute the major reservoir for K in the body, pK may increase markedly and attain values up to 8 mEq/L. Upon cessation of exercise, recovering muscles regain lost K by Na-K-ATPase-mediated K uptake. This leads to a normalization of pK, which may be preceded by a temporarily undershooting of pK. Hence, physical exercise may be associated with major pK changes within a few minutes. Concurrently, during physical exercise, cardiac repolarization duration reflected by QT interval adapts to heart rate by becoming shorter during an increase in heart rate and prolonged during return to the resting heart rate. Since the QT adaptation lags behind the heart rate change, the QT interval for a given heart rate during recovery is shorter than during initiation of exercise. This delay has been termed QT hysteresis (16). Abnormal QT adaptation abnormalities have been associated with higher mortality (15) and ventricular fibrillation (34). Autonomic nervous system modulation and the slow-activating delayed rectifier I\(_{Kr}\) current have been shown to affect QT adaptation (32, 33); however, other factors may be involved. It is our hypothesis that the rapid decrease in pK during recovery following exercise may modulate the QT adaptation to heart rate recovery.

Patients with end-stage renal disease (ESRD) may accumulate K due to insufficient capacity for K excretion. Abnormal K regulation may be an important factor for the almost twofold higher risk of sudden death in patients on hemodialysis compared with a population of coronary artery disease (1). Risk of sudden death has been found highest in the 12-h period before hemodialysis and the 12-h period after starting hemodialysis. This may in part be due to electrophysiological changes to cardiac cells since hemodialysis has been associated with increased QTc interval as well as QT dispersion (18), which in turn have been associated with increased risk of cardiac arrhythmias. Furthermore, hemodialysis has been shown to impair QT adaptation to heart rate under nonexercise conditions (12). Controlling K removal during hemodialysis has been shown to decrease arrhythmogenic activity (28) and attenuate the increase in QT dispersion and QTc (2, 11). In patients with ESRD, the Na-K-ATPase activity is reduced (23), and exercise may increase pK up to twofold compared with healthy controls (27). The effect of high pK, from K accumulation over time before a hemodialysis session, on exercise pK variations has to our knowledge not been studied previously. Also, hemodialysis causes significant changes in extracellular volume and electrolytes, whereas intracellular K remains relatively unchanged (2).
Exercise-associated K fluxes in this setting may cause significant alterations in exercise plasma K variations. It is our hypothesis that hemodialysis through removal of K, primarily from the extracellular phase and through derived effects on the Na-K-ATPase, may lead to increased pK variations during exercise.

On this basis, the aims of the present study were to evaluate the effect of hemodialysis on exercise pK dynamics and QT hysteresis, and whether QT hysteresis is associated with the pK decrease during recovery after exercise.

METHODS

Patient population. We included 22 adult patients (>18 yr old) with ESRD undergoing regular hemodialysis three times per week from the Department of Nephrology, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark. The present study was evaluated and approved by the regional Science Ethics committee (KF 01 319759) and conforms to the principles outlined in the Declaration of Helsinki. All patients submitted written consent to participate in the study. Patients served as own controls. The patients were expected to be able to exercise on a cycle ergometer for at least 4–6 min. Exclusion criteria were exercise-induced loss of consciousness, pregnancy, moderate to severe cardiac hypertrophy on echocardiography, angina pectoris, repolarization abnormalities on ECG, and history of myocardial infarction. Patients were screened for inclusion by review of patient record, patient interview, and clinical assessment.

Hemodialysis. Hemodialysis was performed with Gambro 200 and 200S dialysis machines and with Polyflux dialyzer (Gambro, Stockholm, Sweden). Blood flow rate was 200–300 ml/min, and the dialysate flow rate was 500 ml/min. Ultrafiltration rate was kept constant. The dialysate composition was 148–138 mM sodium with a linear profiling, 2.0 mM potassium, 1.25–1.50 mM calcium, 0.5 mM magnesium, 36 mM bicarbonate, 3 mM acetate, and 5.5 mM glucose. The duration of hemodialysis was 3.6 ± 0.1 h.

Exercise sessions. The experiments were carried out on a day when the patient was scheduled for regular hemodialysis and at least 2 days after the previous hemodialysis session. The individual patient was selected as owns control. Patients rested for 20 min before another exercise session was conducted, as described above with exception of reuse of hemodialysis access and ECG electrodes. Two patients experienced mild to moderate dizziness during recovery, but all 22 patients completed the protocol.

Blood sampling and analysis. Blood sampling was performed at baseline, after 2 min at each load, at exhaustion if more than 30 s had elapsed since the previous blood sampling, and at 2, 5, and 10 min after exercise stop. During exercise, blood sampling was performed within 5 s of a work rate increase. Most patients stopped cycling at an increase in work rate. The blood sampling was performed starting with the disposal of an initial aspirate of two times the estimated dead space in the tubing system including needles, central venous catheter if applicable, and three-way-connector. Thereafter, 2 ml of blood were drawn for pK determination using the Pico50 blood sample aspirator (Radiometer, Ballerup, Denmark) and analyzed in an ABL 625 blood analyzer (Radiometer, Ballerup, Copenhagen) immediately after the exercise session. There were no reports of significant hemolysis during analysis of blood samples. Measurements were calibrated to general standards (26). Additionally, for baseline non-K values, 3 ml of blood were drawn in each of three vacuum tubes (Greiner Bio-One, Frekenhausen, Germany) and analyzed for blood hemoglobin concentration and plasma concentrations of sodium, ionized calcium, magnesium, albumin, urea, and creatinine with Roche Hitachi Modular ISE1800/P800/E170 system (Roche Diagnostics, Basel, Switzerland) and Konelab 30i (Thermo Fisher Scientific, Waltham, MA), except for hematology, which was analyzed with Sysmex XE-2100 (Sysmex, Kobe, Japan), and plasma standard bicarbonate concentration, which was derived from the ABL 625 blood analyzer. Following blood sampling, tubing system was flushed with an isotonic NaCl solution volume of approximately two times the dead space. Blood volume decrease during exercise was evaluated using hemoglobin concentrations \( \Delta BV = 1 - \text{hemoglobin concentration (baseline)/hemoglobin concentration (peak exercise)} \).

The patients’ established hemodialysis access was used for the blood sampling. An arterio-venous fistula with arterial blood was used in 12 patients, and a central venous dialysis access with venous blood was used in 10 patients. The difference in pK between arterial and mixed venous blood has previously been found to be small (30). In the present study, pK was not significantly different before exercise, at exhaustion, or during recovery between the two groups. Also, statistically adjusting for blood sampling site did not change the results significantly. Based on these evaluations, it was considered feasible to pool values for further analysis.

ECG data acquisition. ECG was recorded and printed at the same time as blood sampling (10 mm/mV and 25 mm/s). Machine-derived heart rate and QT interval were recorded. QT interval determination was based on a well validated calculation of duration from the first deflection from baseline in the QRS complex to the end of the final segment of the T wave on averaged ECG data (37). The machine-derived values were verified by manual determinations using printed ECGs. The automated algorithm was unable to correctly provide verifiable heart rate and QT interval measurements in one patient. In another patient, the automated algorithm was unable to provide verifiable heart rate and QT interval measurements during exercise. These data were excluded from the analyses. At rest, corrected QT interval was calculated with both Bazett’s and Fridericia’s formulas. At recovery, QT hysteresis was calculated by subtracting recovery QT interval from the heart rate-matched QT interval during exercise (17). Interpolated QT interval from the closest pair of QT interval and heart rate was used when no exact heart rate match was found. The QT hysteresis values during exercise found in the present study were in line with a previous study (4) given the gender distribution.

Statistics. Student’s t-tests were used for testing means. Bonferroni correction was used in multiple comparisons. For nonnormal distributed data, the corresponding non-parametric tests were used. Linear regression using the method of least squares was used for modeling continuous outcome data. Simple and multiple linear regressions were used for single variable and multivariable analyses, respectively. Mixed-design repeated-measurement (RM) ANOVA was used to analyze repeated-measurement data. Values are means ± SE. Two-tailed P values are given. P < 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC).
before and after hemodialysis, respectively. Thus the lowest pK was reached before hemodialysis. After 2 min of recovery, pK was increased by 4% (P < 0.0001). Following hemodialysis, no patients had pK of >5.0 mM, and three patients had plasma K concentration of <3.5 mM. Plasma concentrations of creatinine, urea, and bicarbonate were increased by 4%, 2%, and 30%, respectively, and plasma urea concentration decreased by 8% (9.2 ± 0.7 min vs. 8.5 ± 0.7 min, P = 0.0009; and 116 ± 9 W vs. 107 ± 9 W, P = 0.0002). Baseline pK, plasma magnesium concentration, and plasma ionized calcium concentration were not related to exercise duration or maximum workload. Hemodialysis caused no significant change in relative blood volume decrease and plasma standard bicarbonate concentration decrease during exercise (4.1 ± 0.7 min vs. 8.5 ± 0.7 min, P = 0.0001).

**RESULTS**

**Baseline data.** The mean age of the 22 patients was 47 yr, with a range of 23–87 yr. Fourteen were men and eight were women. Glomerulonephritis was the most common etiology of ESRD (Table 1). High pK was common in patients before hemodialysis (Table 2). Thus pK was >5.0 mM in 11 patients. Hereof, pK was >6.0 mM in three patients. No patient had pK concentration of <3.5 mM. Hemodialysis reduced pK by 25% (P < 0.0001). Following hemodialysis, no patients had pK of >5.0 mM, and three patients had plasma K concentration of <3.5 mM. Plasma concentrations of creatinine, urea, and magnesium were reduced by 57%, 65%, and 17%, respectively, and body weight was reduced by 2% (P < 0.0001). Plasma concentrations of albumin, sodium, and standard bicarbonate were increased by 4%, 2%, and 30%, respectively, and blood hemoglobin concentration was increased by 4% (P ≤ 0.02). Corrected QT interval calculated with Fridericia’s formula (QTcF) was 5% longer after hemodialysis (P = 0.02).

**pK dynamics during exercise.** pK increased during exercise from 5.1 ± 0.2 mM to 6.1 ± 0.2 mM (P < 0.0001) before hemodialysis (pre-hemodialysis) and from 3.8 ± 0.1 mM to 5.1 ± 0.1 mM (P < 0.0001) after hemodialysis (post-hemodialysis) (Fig. 1). Hence, the highest pK during exercise was reached before hemodialysis. After 2 min of recovery, pK had decreased to 5.0 ± 0.2 mM and 4.1 ± 0.1 mM (P < 0.0001) before and after hemodialysis, respectively. Thus the lowest pK during recovery was reached after hemodialysis. These results show a total variation of up to 2.3 mM in pK during exercise before and after hemodialysis, corresponding to a total variation in pK by up to 59%. Following hemodialysis, exercise duration as well as maximum exercise work rate each decreased by 8% (9.2 ± 0.7 min vs. 8.5 ± 0.7 min, P = 0.0009; and 116 ± 9 W vs. 107 ± 9 W, P = 0.0002). Baseline pK, plasma magnesium concentration, and plasma ionized calcium concentration were not related to exercise duration or maximum workload. Hemodialysis caused no significant change in relative blood volume decrease and plasma standard bicarbonate concentration decrease during exercise (4.1 ±

**Table 1. Etiology of end-stage renal disease for the 22 patients included in the study**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>9</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>3</td>
</tr>
<tr>
<td>Obstructive nephropathy</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>2</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>2</td>
</tr>
<tr>
<td>Tubulointerstitial nephropathy</td>
<td>1</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

Etiology was obtained from review of medical records.

**Fig. 1.** Plasma K concentration (pK) during exercise and recovery in end-stage renal disease (ESRD) patients. Values for pK (mM) were determined in 22 ESRD patients before (pre-hemodialysis) and after hemodialysis (post-hemodialysis) during incremental exercise on a cycle ergometer with 2 min at each work rate until exhaustion and during 10 min of recovery. Values are given relative to work rate in Watts (W) as well as to recovery time in minutes (min). Numbers in brackets are number of patients. Only 12 and 10 patients before and after hemodialysis, respectively, exceeded a work rate of 100 W. For these patients, means of pK as well as of work rate were calculated. pK was measured with ion-sensitive electrode technique. See METHODS for further details. Symbols illustrate means, with bars denoting ± SE.

**Table 2. Baseline parameters for the 22 ESRD patients included in the study before (pre-hemodialysis) and after hemodialysis (post-hemodialysis)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Pre-hemodialysis</th>
<th>Post-hemodialysis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>kg</td>
<td>72.1 ± 2.7</td>
<td>70.4 ± 2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>Beats/min</td>
<td>84 ± 2.9</td>
<td>88 ± 3.2</td>
<td>0.14</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td>mmHg</td>
<td>137 ± 3.4</td>
<td>131 ± 5.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure</td>
<td>mmHg</td>
<td>80 ± 2.4</td>
<td>75 ± 3.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Plasma K concentration</td>
<td>mM</td>
<td>5.1 ± 0.2</td>
<td>3.8 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma Na concentration</td>
<td>mM</td>
<td>138 ± 1.0</td>
<td>141 ± 1.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>Plasma Mg concentration</td>
<td>mM</td>
<td>1.05 ± 0.03</td>
<td>0.87 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma ionized Ca concentration</td>
<td>mM</td>
<td>1.15 ± 0.02</td>
<td>1.21 ± 0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Plasma standard bicarbonate</td>
<td>mM</td>
<td>24.7 ± 0.8</td>
<td>31.5 ± 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood hemoglobin concentration</td>
<td>mM</td>
<td>7.7 ± 0.2</td>
<td>8.0 ± 0.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Plasma albumin concentration</td>
<td>µM</td>
<td>42.5 ± 0.9</td>
<td>44.3 ± 1.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Plasma creatinine concentration</td>
<td>µM</td>
<td>832 ± 40</td>
<td>356 ± 19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma urea concentration</td>
<td>µM</td>
<td>21.2 ± 1.3</td>
<td>7.5 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline QTcB, Bazett</td>
<td>ms</td>
<td>441 ± 5</td>
<td>467 ± 13</td>
<td>0.006</td>
</tr>
<tr>
<td>Baseline QTcF, Fridericia</td>
<td>ms</td>
<td>420 ± 5</td>
<td>440 ± 12</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are given as means ± SE. Patient records, blood samples, and ECG were obtained before exercise. Corrected QT interval was calculated using Bazett’s as well as Fridericia’s formulas. See METHODS for further details. ESRD, end-stage renal disease. Two-tailed P values are given. P < 0.05 was considered statistically significant.
The increase in pK during exercise was significantly higher after hemodialysis compared with before hemodialysis as evaluated by two-way RM ANOVA (P < 0.0001) (Fig. 2). Based on mean values for increase in pK during exercise, the increase in pK at a work rate of 100 W was calculated to be 1.0 mM and 1.5 mM before and after hemodialysis, respectively, i.e., an increase of 31% following hemodialysis. After 2 min of recovery, pK had decreased almost similarly before and after hemodialysis (1.1 ± 0.1 mM vs. 1.0 ± 0.1 mM; P = 0.06). However, before hemodialysis, pK was after 2 min of recovery 0.1 mM lower than the preexercise value, whereas after haemodialysis pK was still at this time 0.3 mM higher than the preexercise value (P < 0.0001) (Fig. 1). After 10 min of recovery, pK was 0.1 mM higher than the preexercise value before hemodialysis and 0.2 mM higher than the preexercise value after hemodialysis (P = 0.12).

Pre-hemodialysis pK increase during exercise was negatively linearly correlated with pK before exercise (β = -0.21 ± 0.08, R² = 0.27, n = 22, P = 0.01) (Fig. 3). Similarly, these parameters tended to be correlated after hemodialysis (β = -0.48 ± 0.25, R² = 0.15, n = 22, P = 0.07). Pooling values from pre-hemodialysis and post-hemodialysis exercise sessions, the increase in pK during exercise also correlated with preexercise pK (β = -0.21 ± 0.06, R² = 0.23, n = 44, P = 0.001). Thus the estimated increase in pK during exercise to exhaustion at a preexercise pK of, e.g., 4 mM was 1.3 mM, whereas at a preexercise pK of 6 mM was only 0.8 mM.

The rate of rise in pK was negatively linearly correlated with maximum work rate during the pre-hemodialysis session (β = -0.87 ± 0.25 μmol·l⁻¹·min⁻¹·W⁻¹, R² = 0.38, n = 22, P = 0.002) as well as during the post-hemodialysis session (β = -1.18 ± 0.35 μmol·l⁻¹·min⁻¹·W⁻¹, R² = 0.31, n = 22, P = 0.007). Also, after statistical correction for baseline pK, the rate of rise of pK was statistically associated with maximum work rate during both the pre-hemodialysis session (R² = 0.46, n = 22, P = 0.001) and the post-hemodialysis session (R² = 0.37, n = 22, P = 0.01).

QT hysteresis. QT hysteresis after 2 min of recovery was not significantly different before and after hemodialysis (16 ± 5 ms vs. 11 ± 4 ms; P = 0.35) but was significantly different from zero (P = 0.003 vs. P = 0.01). After 5 min of recovery, QT hysteresis was 4 ± 3 ms and 8 ± 5 ms before and after hemodialysis, respectively (P = 0.33). After 10 min of recovery, QT hysteresis had decreased in the pre-hemodialysis session (5 ± 2 ms vs. 16 ± 5 ms; P = 0.008). Also, a trend to a decrease was seen in the post-hemodialysis session (3 ± 3 ms vs. 11 ± 4 ms; P = 0.07). The decrease in pK after 2 min of recovery was a determinant of QT hysteresis in the pre-hemodialysis session as QT hysteresis decreased by 38 ± 12 ms for each 1 mM decrease in pK (R² = 0.36, n = 20, P = 0.006) (Fig. 4). Decrease in pK remained a statistically significant determinant after adjusting for maximum heart rate, maximum work rate, and blood sample technique (R² = 0.43, n = 20, P = 0.01). None of these other variables was significantly associated with QT hysteresis. Thus, during recovery, low pK was associated with relatively longer QT interval. In the corresponding analysis for the post-hemodialysis session, QT hysteresis tended to be correlated with the decrease in pK during recovery (P = 0.10). Also, after data were pooled from both sessions, QT hysteresis was negatively linearly correlated with the decrease in pK during exercise (β = -28 ± 9 ms/mM, R² = 0.20, n = 40, P = 0.004).

DISCUSSION

New major findings are an accentuated increase in pK during exercise after hemodialysis and an association between pK and QT interval adaptation during recovery. High pK was associated with an attenuated increase in pK during exercise. The absolute decrease in pK after 2 min of recovery and QT hysteresis was not affected by hemodialysis.

Comparing the ESRD patients before and after hemodialysis, we were able to assess the exercise-induced pK variations over a wide spectrum of preexercise pK values. Differences in
Each symbol represents one pair of measurements. Regression line for all found for the in pK during exercise (3). However, this effect has not been nonspecific skeletal muscle Na-K-ATPase activity (7, 8). In agreement, catecholamines and insulin during hyperkalemia may increase in plasma K concentration. Moreover, increased levels of Na-K-ATPase activity may contribute to an attenuated increase in extracellular volume, K release from working skeletal muscle, and Na-K-ATPase-mediated K uptake. The reduction in the extracellular volume by at most 10–15% due to hemodilysis, given that the entire 2-kg reduction in body weight was fluid removed from the extracellular volume, may only explain up to half the additional increase in pK during exercise after hemodialysis with an unaltered K flux. Thus reduced K gradient between the extracellular and intracellular phases in hyperkalemia and increased K uptake due to K stimulation of the Na-K-ATPase activity may contribute to an attenuated increase in plasma K concentration. Moreover, increased levels of catecholamines and insulin during hyperkalemia may increase skeletal muscle Na-K-ATPase activity (7, 8). In agreement, nonspecific β-adrenoceptor blockade accentuates the increase in pK during exercise (3). However, this effect has not been found for the α-adrenoceptor blocker doxazosin or for the nonselective α-adrenoceptor and β-adrenoceptor blocker carvedilol with exercise at moderate work load (20, 21), which may be due to α-adrenoceptor-mediated K release and differences in work load. Although plasma standard bicarbonate concentration was higher after hemodialysis, bicarbonate buffering of acid equivalents during exercise remained stable between the two sessions, indicating no major difference in acid-base-induced K shifts. Furthermore, the relative pK after 10 min of recovery was similar following hemodialysis, indicating no major equilibration of K from the intracellular to extracellular phase during the exercise session following hemodialysis. In addition to an attenuated pK before hemodialysis, the accentuated increase in pK during exercise after hemodialysis may reflect an increased K gradient and a non-augmented, decreased Na-K-ATPase-mediated K uptake. This is consistent with the relatively blunted decrease in pK during recovery following hemodialysis. In hyperkalemia, the attenuated increase in pK during exercise confers relative protection against a further increase of pK to deleterious high levels. In experimental animals, we previously found protection against β-adrenoceptor agonist reduction of pK in severe hypokalemia (35). Thus, taken together, it seems that homeostatic mechanisms provide some protection against severe hyperkalemia as well as hypokalemia.

Exercise capacity was, in the present study, negatively correlated with pK increase as well as pK rate of rise during exercise. Correspondingly, impaired K homeostasis in patients with ESRD has been suggested as a possible factor of decreased exercise performance (22, 27). At variance, another study found no difference between patients with ESRD and normal controls (7). In the present study, the large range in amplitude and rate of rise in pK during exercise as well as in exercise capacity indicate that impaired K homeostasis may not be an intrinsic feature of ESRD. Training status may be an important covariate (19). Exercise training has previously been associated with improved performance and improved K homeostasis in patients with ESRD (22) as well as in normal subjects (19). In the study on patients with ESRD, the effect of differences in preexercise pK was not taken into account when groups were compared. This may have led to an underestimation of the effect of training on the K homeostasis. In addition to training status, another covariate may be the temporal relation to hemodialysis as exercise duration and maximal work rate were reduced following hemodialysis despite lower pK. Acute hemodynamic effects of pK changes (10) as well as a state of nonequilibrium following hemodialysis (6) may increase muscle fatigue during exercise following hemodialysis.

To our knowledge, this is the first time an association between QT hysteresis and decrease in pK during recovery following exercise has been observed. Thus the present study provides evidence of a relationship between pK and QT interval beyond resting conditions (11). It indicates that the sudden and large decrease in pK in the recovery phase following exercise may modulate the QT interval. Although it is not possible to infer causality, it is noteworthy that both QT hysteresis and pK decrease during the early phase of recovery were unchanged by hemodialysis. The decreased QT hysteresis with large decreases in pK during recovery aligns well with a previous report of shortening of the QT interval by K supplementation (5). Interestingly, β-adrenoceptor antagonists have been associated with normalization of the QT hysteresis and prevention of arrhythmia in patients with long QT syndrome (17). Apart from a modulation of the I_kr current, the Na-K-ATPase as a major determinant of pK and QT adaptation may be an important factor. In the heart, impaired Na-K-ATPase activity impedes slow-phase QT adaptation (24). The estimated time for 90% action potential duration adaptation of 3.5 min is within the time domain investigated in the present study. Furthermore, during exercise-associated hyperkalemia and reduced Nernst potential, the augmented Na-K-ATPase pump current may constitute a more significant part of the repolar-

Fig. 4. Relationship between decrease in pK and QT hysteresis at 2 min of recovery after exercise. Values for pK (mM) were determined before (pre-hemodialysis) and after hemodialysis (post-hemodialysis) during 10 min of recovery after exercise. Values for QT interval (ms) were derived from ECG recorded simultaneously with blood sampling. QT hysteresis was calculated by subtracting QT interval after 2 min of recovery from heart rate-matched QT interval during exercise. See legends to Fig. 1 and METHODS for further details. Each symbol represents one pair of measurements. Regression line for all points has been drawn.
izing current. At rest, the same degree of hyperkalemia may, particularly in settings with concurrent hypocalcaemia, have a more deleterious effects (9).

Through modulation of QT adaptation and cardiac repolarization, the Na-K-ATPase and K dynamics may be important beyond the setting of ESRD. Previously, we found high atrial Na-K-ATPase concentration as well as high increase in pK to be risk factors for the development of atrial fibrillation (36). Furthermore, it has been suggested that dysfunctional Na-K-ATPase intracellular trafficking may be involved in long QT syndrome (31). Exercise and pK variations have been associated with sudden death (8). Recently, QTc interval has been shown to be increased concurrent with hypokalemia immediately after marathon running in healthy men (29), supporting an association between pK and cardiac repolarization in an exercise setting. On the other hand, exercise training increases muscular Na-K-ATPase concentration (19) and improves QT adaptation during exercise (25), which may protect against arrhythmias. Taken together, the present results provide additional evidence to support the importance of exercise K homeostasis for cardiac repolarization. This suggests that the heart may be sensitive to pK variations during exercise and recovery. Abnormal exercise K homeostasis as well as sympathetic activation may, through modulation of cardiac repolarization, be an important general mechanism that primes potential arrhythmia substrates, triggering arrhythmia.

In conclusion, the present study shows an accentuated increase in pK during exercise after hemodialysis, an attenuated increase in pK during exercise with hyperkalemia, and an association between pK and QT interval adaptation during recovery. The large variation in pK around the time of hemodialysis with hyperkalemia initially and the subsequent removal of K from primarily the extracellular volume may, especially in the setting of superimposed exercise-induced pK variations, be associated with significant effects on cardiac repolarization. Furthermore, the association between pK and QT interval adaptation suggests that the heart may be sensitive to the major variation in pK during exercise. Thus acute pK variations induced by exercise and hemodialysis may be a trigger of cardiac arrhythmias.

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AUTHOR CONTRIBUTIONS


REFERENCES


