Effects of endurance training on extrarenal potassium regulation and exercise performance in patients on haemodialysis

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Abstract

Background. Haemodialysis patients (HDP) with anaemia display impaired plasma K⁺ regulation during exercise and poor exercise performance. Epoetin treatment and exercise training improve exercise performance in HDP, but whether this is associated with improved K⁺ regulation is unknown.

Methods. Six HDP with near-normal [Hb] were tested for aerobic power (VO₂peak) and plasma [K⁺] during incremental exercise; quadriceps muscle strength (peak torque, PT) from 0 to 360° s⁻¹ and fatiguability (decline in strength during thirty contractions). Tests were conducted at baseline, after 6 weeks of normal activity (pre-train) and following 6 weeks cycle training (post-train). Six healthy untrained controls (CON) matched for age, sex, mass and height were tested at baseline.

Results. In HDP at baseline, VO₂peak and PT from 0 to 360° s⁻¹ were respectively reduced by 37% and 27–42%, compared to CON (P < 0.05). Plasma [K⁺], the rise in [K⁺] (Δ[K⁺]) and the Δ[K⁺] relative to total work done (Δ[K⁺] work⁻¹) during incremental exercise were all higher in HDP at baseline compared to CON (P < 0.05). Exercise training increased time to fatigue by 12% (P < 0.05) but did not improve K⁺ regulation or VO₂peak. An inverse correlation was found between the Δ[K⁺] work⁻¹ ratio and VO₂peak for pooled CON and HDP data.

Conclusions. In HDP treated with epoetin, poor exercise performance was related to impaired extrarenal K⁺ regulation, whilst training improved exercise performance but not K⁺ regulation. Thus, although impaired extrarenal K⁺ regulation may contribute to poor exercise performance in HDP, exercise performance can still improve with training despite unchanged K⁺ regulation.

Keywords: exercise training; haemodialysis; muscle strength; potassium regulation; VO₂peak

Introduction

Haemodialysis patients (HDP) display abnormally low exercise performance, with peak oxygen consumption during incremental exercise (VO₂peak) and muscle strength each...
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Reduced by up to 50% compared to healthy controls (CON) [1,2]. Anaemia contributes to reduced exercise performance in HDP [3,4]. However, normalization of haemoglobin concentration ([Hb]) with epoetins (ESA) does not normalize VO_{peak} [3,4]. Thus, other factors must also be involved. HDP showed an exaggerated rise in arterial [K+] to ~7 mM during incremental exercise, which was inversely correlated with VO_{peak} [1]. Furthermore, patients with chronic kidney disease have a reduced muscle membrane potential at rest [5,6] and during exercise [6]. Together, these findings suggest that reduced muscle membrane excitability, caused by impaired muscle K⁺ regulation, may contribute to the poor exercise performance in HDP. Few studies have compared extrarenal K⁺ regulation during exercise between HDP and CON and in those studies all patients had severe anaemia [1,7,8]. A relationship was identified between [Hb] and plasma K⁺ regulation during exercise in HDP, in whom exercise-induced hyperkalaemia was ameliorated after treatment with ESA [4]. Furthermore, ESA treatment is known to increase Na⁺,K⁺-ATPase activity in rat myocardium [9]. Thus, ESA treatment may improve the impaired extrarenal K⁺ regulation [4] in HDP [1,8]. Although, whether such regulation remains impaired in ESA compared to CON is unknown. This study therefore investigated muscle function, aerobic power (VO_{2peak}) and plasma [K⁺] during incremental exercise in HDP with near-normal [Hb] and in CON. The first hypothesis tested was that, despite chronic treatment with ESA, HDP would still exhibit reduced muscle function, VO_{2peak} and elevated plasma [K⁺] during exercise compared to CON.

Exercise training lowers the exercise-induced rise in plasma [K⁺] in healthy subjects [10–12] and in chronic heart failure patients [13]. If extrarenal K⁺ regulation is also improved in HDP following training, this may contribute to their improved exercise performance [14,15]. Therefore, this study also measured the effects of cycle training on muscle function, aerobic power and plasma [K⁺] during incremental exercise in HDP and hypothesized that each would be improved with training.

Methods

Study design

HDP initially performed a familiarization trial, then two trials to determine within-subject variability of knee-extensor strength and fatiguability tests. The familiarization and variability trials were performed at least 1 week apart and 1 week prior to the experimental trials. Experimental trials were conducted at baseline, again after 6 weeks of normal daily activity (pre-train), and following 6 weeks of stationary cycle ergometer training (post-train). Thus, the baseline to pre-train interval acted as a within-subject control period. In addition to the strength and fatiguability tests, subjects also completed a maximal incremental exercise test at baseline, pre-train and post-train to determine VO_{2peak} and plasma [K⁺]. All tests were performed on a non-dialysis day, the same length of time after the patients last dialysis session (baseline 22 ± 9, pre-train 20 ± 9, post-train 21 ± 8 h post-dialysis, mean ± SD). The final tests were conducted within 3 days (range 1–3, 1.3 ± 0.8 days) of completing training. Sedentary healthy control subjects (CON), matched for age, sex, body mass and height, also performed all baseline tests.

Subjects

Eight HDP and six CON gave written informed consent and agreed to participate (Table 1). One HDP was excluded due to an abnormal ECG during

<table>
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<tr>
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<tr>
<td>Epoetin (units kg⁻¹·week⁻¹)</td>
<td>6</td>
<td>102 ± 61</td>
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<tr>
<td>Metoprolol (mg day⁻¹)</td>
<td>2</td>
<td>75 ± 35</td>
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<tr>
<td>Irbesartan (mg day⁻¹)</td>
<td>1</td>
<td>300</td>
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<tr>
<td>Amlodipine (mg day⁻¹)</td>
<td>3</td>
<td>6.7 ± 2.9</td>
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<tr>
<td>Prednisolone (mg day⁻¹)</td>
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Values are mean ± SD.

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Values are mean ± SD.

Subjects aged 18–65 years, at least 6 months of ESA treatment and in a stable clinical state at the time of experimentation were enrolled. Exclusion criteria included symptomatic ischaemic heart disease, peripheral vascular disease, disabling arthritis, chronic airflow obstruction, or pregnancy. Medications (Table 2) remained constant throughout the study duration. This study was approved by the Human Research Ethics Committees at Victoria University and Melbourne Health.

Exercise tests

Aerobic power (VO_{2peak}). Subjects cycled at or above 60 rpm on an electrically braked cycle ergometer (Lode, Groningen, Holland) at an initial power output of 15 W with progressive increments of 15 W each minute. Subjects continued until volitional fatigue, defined as an inability to maintain cadence at or above 60 rpm. Expired O₂ and CO₂ and ventilation were continuously measured [16].

Quadrieps strength test (torque–velocity relationship). Subjects performed three maximal quadriceps muscle contractions at velocities of 0 (isometric), 60, 120, 180, 240, 300 and 360 °s⁻¹, with 60 s recovery between sets, on an isokinetic dynamometer (Cybex Norm 770, Henley HealthCare, Massachusetts) [16]. The highest of each set of three was defined as peak torque (PT).

Quadrieps fatigue test. To induce local muscular fatigue, subjects performed 30 maximal quadriceps muscle isokinetic contractions at 180 °s⁻¹, with ~1 s pause between repetitions. Fatigue index (FI) was calculated as the percent decline in torque [16]. Fatigue test data were excluded for one subject due to highly variable and unreliable results.

Blood sampling and processing. Blood was sampled during the aerobic power test from the arterio-venous fistula in HDP, and from a dorsal hand vein in CON (arterialized venous blood), after heating the hand in a 45°C water bath [10]. Blood was analysed in duplicate for [Hb] and haematocrit.
Exercise training

HDP trained on a stationary cycle ergometer (Monark 868, Vansbro, Sweden) for 30 min during the first hour of their haemodialysis treatment, three times per week for 6 weeks. Each training session comprised a 5-min warm-up at 25 W, 20 min of cycling at the training work rate and a 5-min warm-down at 25 W. The training intensity started at a work rate corresponding to 50% of the pre-train VO₂peak and was increased by 10% of the preceding value each week, being 50, 55, 60.5, 66.6, 73.2 and 80.5% of pre-train VO₂peak for Weeks 1–6, respectively. This training intensity previously increased VO₂peak in HDP by ~20% [18,19].

Statistics

Data are presented as mean ± SD. A one-way ANOVA was used to detect differences between CON and HDP at baseline, pre-train, and post-train, except for [K⁺] data, for which a two-way ANOVA (group/training status, sample time) was used. The least significant difference test was used for post hoc comparisons. A paired r-test was used to compare initial and final training work rate. Correlations were determined by least squares linear regression. Statistical significance was accepted at P < 0.05. Effect size (ES, partial eta squared) was determined for ANOVA to determine the magnitude of effects. The coefficient of variation (CV) between baseline and pre-train was calculated to determine the stability of the exercise tests during the non-training period. Statistical analyses were performed using SPSS version 15.

Results

Exercise tests

Subject physical characteristics. Age, body mass, height, BMI and Hct did not differ between HDP and CON; however [Hb] in HDP was ~19g L⁻¹ (13–15%) less than in CON (Table 1). HDP physical characteristics did not change during the course of the study (Table 1).

Variability of exercise tests. The within-subject CV during the variability trials for the isometric PT and FI was 2.6 ± 1.2% and 4.4 ± 2.5%, respectively. In HDP, the variability from baseline to pre-train was 8.9 ± 3.2% for VO₂peak, 5.3 ± 3.8% for time to fatigue (TTF), 9.2 ± 7.6% for work done during incremental exercise, 5.4 ± 3.7% for knee-extensor isometric PT and 5.0 ± 5.2% for fatigue index. Thus typical variability was observed for all tests.

Training work rate. The mean training work rate increased by 65% (P = 0.002) from the first (43 ± 11 W) to the last (71 ± 22 W) training session.

Quadriceps strength. Muscle PT (Nm) was depressed at all velocities in HDP compared to CON, at each of baseline, pre-train and post-train (Figure 1). When expressed relative to body mass (Nm kg⁻¹), PT was still depressed in HDP at each timepoint, from 60 up to 360° s⁻¹ (Figure 1). In HDP, PT was not changed after training, except at one contraction velocity (180° s⁻¹), which was higher at post-train compared to baseline and tended to be higher than pre-train (Nm, P < 0.06, ES = 0.57, power = 0.80) and when expressed relative to body mass (Nm kg⁻¹, P < 0.06, ES = 0.54, power = 0.75).

Aerobic power. HDP had lower VO₂peak, TTF and work done during incremental exercise at baseline compared to CON, by 37, 46 and 69%, respectively (Table 3). Both TTF and work performed were stable between baseline and pre-train with each increased with training, whereas VO₂peak was unchanged (Table 3).

Plasma [K⁺]. Exercise increased plasma [K⁺] (P < 0.001, Figure 2). Plasma [K⁺] was higher in HDP at baseline and pre-train compared to CON before, during and after exercise (Figure 2). Whilst plasma [K⁺] did not differ significantly pre- and post-training (P < 0.20, ES = 0.36), after training, plasma [K⁺] was no longer different between HDP and CON.

The rise in [K⁺] (Δ[K⁺]) at common submaximal work rates was higher in HDP at baseline than in CON, but Δ[K⁺] at fatigue was similar (Figure 2). The Δ[K⁺] relative to work done (Δ[K⁺]/work⁻¹) was higher in HDP than in CON at baseline (240%, P < 0.001), pre-train (180%, P < 0.005)
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Table 3. $\text{VO}_2\text{peak}$, time to fatigue and work done during the aerobic power test

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<tr>
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<th>CON</th>
<th>HDP</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Pre-train</td>
</tr>
<tr>
<td>Time to fatigue (s)</td>
<td>950 ± 224</td>
<td>511 ± 139†</td>
</tr>
<tr>
<td>Work done (kJ)</td>
<td>125.4 ± 51.6</td>
<td>38.6 ± 20.2*</td>
</tr>
<tr>
<td>$\text{VO}_2\text{peak}$ (ml kg$^{-1}$ min$^{-1}$)</td>
<td>37.4 ± 4.7</td>
<td>23.5 ± 7.7*</td>
</tr>
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Values are mean ± SD; n = 6 per group.
*CON, (P < 0.05).
†>Baseline, (P < 0.05).
‡‡>Pre-train (P < 0.05).

![Fig. 2.](image)

**Correlations.** No significant correlations were found between $\Delta [K^+]$ or the $\Delta [K^+]$ work$^{-1}$ ratio and any of the exercise variables for CON or for HDP at baseline, pre-train or post-train (each $n = 6$). However, when CON and the baseline data for HDP were pooled ($n = 12$), strong in-

verse correlations were found between the $\Delta [K^+]$ work$^{-1}$ ratio and each of $\text{VO}_2\text{peak}$ ($r = -0.83, P < 0.001$, Figure 4), peak work rate ($r = -0.72, P < 0.01$) and time to fatigue during the aerobic power test ($r = -0.70, P < 0.05$). A strong positive correlation was found between the $\Delta [K^+]$ work$^{-1}$ ratio and FI ($r = 0.67, P < 0.05$, Figure 4).

**Discussion**

Extrarenal plasma $[K^+]$ regulation is impaired in HDP

The first novel finding of this study was that, despite treatment with ESA, HDP patients exhibited impaired extrarenal $K^+$ regulation during incremental exercise, with higher plasma $[K^+]$ (18–33%) in HDP at baseline compared to CON. Due to the higher plasma $[K^+]$ at rest in HDP, the $\Delta [K^+]$ was calculated, and was 10% higher in HDP than in CON. CON completed significantly more work than HDP during incremental exercise, so the $\Delta [K^+]$ work$^{-1}$ was also calculated [10] and was greater by 239% in HDP than in CON. This finding supports and extends our previous study in anaemic HDP [1]. All of these variables were improved by ∼50% in these ESA-treated HDP, compared to the non-ESA-treated HDP [1]. This may be explained by the ESA treatment directly, as the rise in plasma $[K^+]$ during exercise in HDP was ameliorated after 4 weeks of ESA treatment.
possibly due to stimulatory effects of ESA on the muscle Na⁺,K⁺-ATPase [9]. Alternatively, it might be linked to the higher [Hb], as the ESA-treated HDP in this study had ~70% higher [Hb] than the anaemic HDP in our previous study (12.9 ± 0.8 versus 7.8 ± 1.2 g dL⁻¹, P < 0.0001). The persistent impairment of plasma K⁺ regulation observed here might be due to reduced Na⁺,K⁺-ATPase activity in skeletal muscle in HDP, as we have recently described [20]. Patient medications are unlikely to have affected plasma [K⁺], as only β₁-blockers were taken by HDP in this study, which do not affect plasma [K⁺] during exercise [21]. Two patients were taking low doses of prednisolone. Prednisolone increases skeletal muscle Na⁺,K⁺-ATPase content in humans [22], which might lower plasma [K⁺] during exercise and thus reduce the difference between HDP and CON. However, treatment with dexamethasone, a more potent glucocorticoid than prednisolone, increased skeletal muscle Na⁺,K⁺-ATPase activity and content [23] but had no effect on thigh muscle K⁺ release during high intensity exercise [24]. Additionally, the plasma [K⁺] of the patients taking prednisolone in this study was within the range of the other patients, suggesting little, if any, drug effect.

Surprisingly, training did not significantly improve acute K⁺ regulation in HDP. However, there was a tendency for improved K⁺ regulation after training, as the post-train plasma [K⁺] in HDP was not different from CON and the post-train Δ[K⁺] work⁻¹ ratio tended to be lower than pre-train (P = 0.10, ES = 0.51). Given the moderate effect size, it could be that the lack of a training effect on plasma K⁺ regulation is due to a type II error. However, an insufficient training intensity cannot be ruled out.

If elevated extracellular [K⁺] does contribute to muscle fatigue, it might be expected that fatigue would occur at similar plasma [K⁺] in HDP and CON. However, plasma [K⁺] at fatigue was greater in HDP at baseline and pre-train than in CON. It is important to note that arterialized-venous and arterial plasma [K⁺] underestimate, and may not accurately reflect [K⁺], in the interstitium [25,26], which is the site where [K⁺] is likely to have an effect.

The different blood sampling sites used in HDP (arterial) and in CON (arterialized-venous) is unlikely to have affected these results, since arterialized venous plasma [K⁺] has been shown not to differ from arterial [K⁺] during low to moderate intensity exercise, and was only marginally higher (4%) during high intensity exercise [27]. Increasing the arterialized venous plasma [K⁺] in CON by 4% had no effect on the differences between HDP and CON (data not shown). Thus, differences observed between HDP and CON on plasma [K⁺] do not appear related to methodological factors.

**HDP display greater fatiguability, impaired VO₂peak and muscle strength**

This study shows that VO₂peak (40%) and knee-extensor peak torque (27–42%) were reduced in ESA-treated HDP compared to CON. These deficits are similar to those previously reported in chronically ESA-treated HDP for VO₂peak [3,18] and muscle strength [2,6,28]. PT was still reduced by 15–36% when expressed relative to body mass. The poor PT observed in HDP may be due to reduced muscle mass, as it has been shown that lower leg strength is normalized when expressed relative to muscle cross-sectional area (CSA) [6,28]. As muscle CSA was not measured, this cannot be confirmed in the present study. Muscle strength was unchanged following training, which is not surprising as endurance-based training programs typically do not enhance muscle strength, although improved muscle strength following 2 months of cycle training has previously been observed in HDP [14,18].

This is the first report of muscle fatiguability following dynamic contractions in HDP. Knee-extensor FI was higher in HDP than in CON. This is consistent with the 300% higher fatiguability following repeated isometric dorsiflexor contractions [6], and 10% higher handgrip fatiguability [29] compared to CON. Training did not increase FI in the present study, which contrasts a recent study that found a 40% increase in fatigue resistance during submaximal leg
press following 2 months of cycle training in HDP [18]. Together, with the finding of increased time to fatigue after training in the present study, these results suggest that endurance training decreases fatigability during submaximal but not maximal contractions in HDP.

An interesting finding was that time to fatigue and total work performed during incremental exercise were each increased following training, yet no improvement in $V_{O2}^{peak}$ was found. These HDP patients displayed large functional deficits, with severely reduced $V_{O2}^{peak}$ and muscle strength and should have been highly responsive to exercise training. However, many studies have found little effect on $V_{O2}^{peak}$ after training [30–34]. This was corroborated by a similar lack of change after ~7 months of training [32]. It is possible that exercise training results in improved mechanical efficiency, which prolongs exercise time despite a possible central limitation to $V_{O2}^{peak}$ that is not improved. Nonetheless, it remains possible that the lack of change in $V_{O2}^{peak}$ was due to a type II error or an insufficient training intensity or duration. Further research is warranted to identify the mechanisms underlying the lack of improvement in $V_{O2}^{peak}$ after training in some HDP.

A link is suggested between poor exercise performance and impaired K$^+$ regulation in HDP, by significant inverse correlations between the $\Delta [K^+]$ work$^{-1}$ ratio and each of $V_{O2}^{peak}$, time to fatigue and peak work rate during the aerobic power test, as well as $PT$ at 0° $s^{-1}$. This supports our previously reported inverse correlation between the $\Delta [K^+]$ work$^{-1}$ ratio and $V_{O2}^{peak}$ in HDP that were not treated with ESA [1]. Furthermore, the positive correlation with knee-extension fatigability (when CON and baseline HDP data were pooled) suggests a local muscular origin of fatigue, which limits aerobic exercise performance, possibly related to poor muscle K$^+$ regulation.

This study has several limitations. The participants in this study were relatively healthy and well motivated, reflecting the exclusion criteria to satisfy maximal exercise testing requirements. Hence, the exercise performance of the general HDP population is likely to be considerably worse than indicated in this study. The small sample size of this study reflects the difficulty in recruiting HDP without significant comorbidities, which is confounded by the increasing incidence of diabetes in these patients. Due to the recruitment difficulties, this study lacked a non-training HDP group. Thus, any improvement in exercise performance following training could potentially have been due to a familiarization effect. This seems unlikely, however, since increases in time to fatigue and work done between pre-train and post-train were larger than the CV for these measures, indicating that these increases were a true training-induced adaptation. Plasma [K$^+$] showed a small but non-significant decrease from baseline to pre-train. Although familiarization may affect exercise performance or muscle strength, it would be extremely unlikely to reduce plasma [K$^+$] at rest and during submaximal exercise. This is because the major determinants of plasma [K$^+$] during exercise are the exercise intensity and muscle mass, which are then modified by physiological factors such as muscle activation, Na$^+$, K$^+$-ATPase, adrenaline levels, etc. It is possible that this small decrease was due to an increase in the patients’ physical activity levels from baseline to pre-train. Unfortunately, physical activity levels were not objectively assessed. Finally, the [Hb] of the HDP was still low compared to CON, which may have contributed slightly to their poor exercise performance and impaired K$^+$ regulation. This difference in [Hb] does, however, reflect the current clinical practice of maintaining [Hb] at ~120 g L$^{-1}$ in otherwise healthy HDP.

**Summary**

Compared to healthy controls, HDP treated long-term with ESA had substantially poorer exercise performance, which was related to their impaired extrarenal K$^+$ regulation. Endurance training in HDP improved time to fatigue during an incremental cycle test but did not enhance $V_{O2}^{peak}$ or plasma K$^+$ regulation. Thus, impaired extrarenal K$^+$ regulation may contribute to the poor exercise performance in HDP; however, exercise performance improved with training despite unchanged K$^+$ regulation.

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Conflict of interest statement. None declared.

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