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Original Article

Physical performance and associated electrolyte changes after haemoglobin normalization: a comparative study in haemodialysis patients

Lawrence P. McMahon[1], Michael J. McKenna[2], Termboon Sangkabutra[3], Kim Mason[1], Simon Sostaric[2], Sandford L. Skinner[4], Caroline Burge[4], Brendan Murphy[1] and David Crankshaw[4]

[1]Department of Nephrology, The Royal Melbourne Hospital, Parkville, [2]Department of Human Movement, Recreation and Performance, Centre for Rehabilitation, Exercise and Sports Science, Victoria University of Technology, Melbourne, [3]Anaesthetic Research and Education Unit, Department of Pharmacology, and [4]Department of Physiology, University of Melbourne, Parkville, Victoria, Australia

Abstract

Background. To determine the effects of different haemoglobin (Hb) levels on exercise performance and associated electrolyte changes, a prospective, randomized, double-blinded crossover study was completed in 14 haemodialysis patients.

Methods. Performance and changes in arterial $[K^+]$ and lactate were compared at rest and during a maximal incremental cycling exercise at a Hb concentration ([Hb]) of 10 g/dl ($[Hb]_{10}$) and 14 g/dl ($[Hb]_{14}$) following an initial baseline test (Hb: 8.3 ± 0.2 g/dl, mean $\pm$ SEM). Ages ranged from 23 to 65 years and patients were divided into younger (age 23–45 years, $n=9$) and older (aged 55–65 years, $n=5$) groups.

Results. Peak work rate and V_{02} peak were higher at $[Hb]_{14}$ than at $[Hb]_{10.}$ 145 ± 9 *vs* 134 ± 9 W, $\mu \pm$ SEM, $P<0.01$, and 1.90 ± 0.11 *vs* 1.61 ± 0.11 l/min, $P<0.01$, respectively. Improvements were demonstrated in both younger and older groups at the higher target [Hb], with an improved aerobic performance evident particularly in younger patients. However, performance remained below that predicted for comparable sedentary controls. Resting plasma $[K^+]$ was raised at both $[Hb]_{10}$ and $[Hb]_{14}$ compared with baseline ($P<0.01$) although the change in $[K^+]$ from rest to peak exercise ($\Delta[K^+]$) was similar at each level. The $\Delta[K^+]$ per unit work performed (used as a marker of K^+ regulation) was, however, inversely related to the [Hb] (baseline: 80 ± 12 μmol/l/kJ *vs* $[Hb]_{10.}$ 61 ± 8, $P<0.01$, *vs* $[Hb]_{14.}$ 49 ± 7, $P<0.05$). Exercise induced a significant but similar rise in lactate concentration at both target [Hb] ($P<0.001$), which remained markedly elevated for at least 10 min after exercise in both younger and older groups.

Conclusions. These data demonstrate that a physiological [Hb] improves, but does not normalize, exercise performance in end-stage renal failure. Both younger and older patients appear to benefit similarly from the enhanced oxygen transport. Impaired K^+ regulation is apparently related to [Hb] and could well contribute to the observed limitations in performance.

Key words: epoetin; exercise; haemodialysis; normal haemoglobin; potassium

Correspondence and offprint requests to: L. P. McMahon, Department of Nephrology, The Royal Melbourne Hospital, Parkville, Victoria 3052, Australia.

Introduction

Exercise performance in patients with end-stage renal failure (ESRF) improves substantially after partial correction of anaemia [1–5] but remains well below normal. Whether this is due to incomplete correction of anaemia or to other factors is unclear. Although available data suggest that limitations in performance remain regardless of haemoglobin concentration ([Hb]) [6–8], controlled normalization studies have not been reported.

A variety of factors other than anaemia could limit exercise performance in ESRF [8–10]. Systemic conditions such as concurrent disease, malnutrition and a profoundly sedentary lifestyle are undoubtedly significant in many patients. It is also apparent, however, that specific muscle abnormalities, due either to ESRF or anaemia itself, might also be important [8,11,12].

Potassium (K^+) has not yet been recognized as contributing to impaired exercise performance in ESRF [13] although loss of K^+ from contracting muscle in healthy subjects has been associated with fatigue [14,15] and patients with ESRF frequently demonstrate hyperkalaemia. The latter is often attributed to dietary indiscretion, however, there is also indirect evidence that K^+ homeostasis might be impaired in uraemia secondary to reduced Na^+K^+-ATPase activity in

skeletal muscle and other tissues [16–19]. Because of the central role of this enzyme in K^+ regulation, particularly during exercise [14,15], it is possible that impaired activity also contributes to limitations in exercise capacity in ESRF. Furthermore, low epoetin levels have been associated with depressed Na^+K^+-ATPase activity [20].

It was therefore hypothesized that normalization of [Hb] (compared with subnormal correction) in sedentary, but otherwise healthy, ESRF patients would improve but not normalize exercise performance and K^+ homeostasis.

Subjects and methods

Patients

Thirty stable, sedentary, haemodialysis patients without cardiovascular, respiratory or musculoskeletal disease were enrolled in a double-blinded, prospective, crossover study using epoetin to compare aerobic performance and electrolyte and acid–base changes during maximal exercise testing at two levels of [Hb]: 10 ($[Hb]_{10}$) and 14 ($[Hb]_{14}$) g/dl.

Fourteen patients completed the study and were eligible for analysis (one died, six received a cadaveric transplant, one withdrew with significant uraemic bone disease, two were withdrawn because of poor compliance and six elected not to continue). Antihypertensive medication during the study included eight patients on no therapy, angiotensin converting enzyme inhibitors in three patients and calcium-channel blockers in three patients.

Subjects had been on dialysis for at least 12 months [34 ± 29 months, μ (mean) ± SD, range 12–59 months] and were randomly assigned to one of the two target [Hb]. They were maintained at this level for 4 weeks before testing was performed. The procedure was then repeated after patients had achieved the alternate [Hb] (Figure 1). Baseline mean [Hb] was 8.3 ± 0.2 g/dl.

Patients acted as their own controls and for analysis were also divided into two groups: younger (34 ± 10 years, μ ± SD, range 23–45 years, $n = 9$) and older (58 ± 4 years, μ ± SD, range 55–66 years, $n = 5$) (Table 1). All patients ($n = 14$) were compared with predicted sedentary norms matched for age and weight [21,22].

All procedures were approved by the Royal Melbourne Hospital Board of Medical Research Advisory Committee and the Victoria University of Technology Human Research Ethics Committee. All patients gave informed consent.

Methods

Exercise test

Initial (pre-Epoetin) testing comprised a maximal incremental exercise test to establish peak exercise performance, to obtain some baseline data points for subsequent comparison (non-performance related) and for familiarization. For each patient tests were performed on the same day of the week at a constant time relative to the previous dialysis (6–42 h post-dialysis). Heart rate and rhythm were monitored during the test using a 12-lead electrocardiogram (Mortara, Boston, MA, USA). Arterial blood pressure was determined by auscultation prior to exercise.

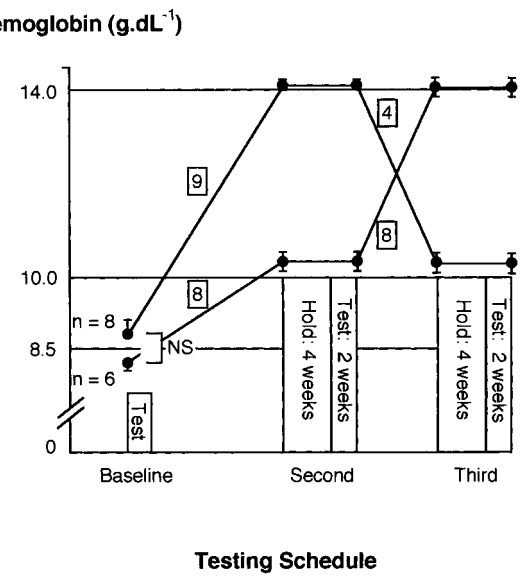

Fig. 1. Outline of study. Boxed numbers, 🄽, indicate the number of months required for all patients to have reached target [Hb]. Time required to reach each target [Hb] did not differ significantly between groups.

Patients sat on an electrically braked cycle ergometer (Lode, Groningen, The Netherlands) for 15 min before commencing cycling. For the baseline test younger subjects commenced pedalling at 25 W with progressive increments of 25 W/min. The pedal cadence was 70 r.p.m. and the test was continued to volitional fatigue, defined as an inability to maintain pedal cadence above 55 r/W/min. Older subjects were exercised similarly except that the work rate was increased by 15 W/min. Patients were encouraged verbally to maintain pedal cadence for as long as possible. In the tests at target [Hb], the work rate was increased according to baseline studies up to the peak initial work rate; thereafter increments were reduced to 15 W/min in younger and 10 W/min in older subjects in order to define peak exercise performance more accurately.

Respiratory measurements

Expired oxygen and carbon dioxide fractions and volume were measured for 15 min prior to exercise, during exercise and for 10 min following (recovery). Subjects breathed through a Hans-Rudolph two-way valve with the expired gas passing through low-resistance plastic tubing into a 4-l mixing chamber. Mixed expired oxygen (O_2) and carbon dioxide (CO_2) concentrations were analysed continuously using rapidly responding O_2 and CO_2 analysers (Ametek S-3A/II and Ametek CD-3A, Pittsburgh, PA, USA). Expired volume was determined using a flow transducer (KL Engineering K520, Sunnyvale, CA, USA). Ventilation (V_E, l/min), oxygen uptake (V_{O2}), carbon dioxide output (V_{CO2}) and gas exchange were then calculated and displayed (Turbofit, Ventura, CA, USA) on an IBM-compatible computer every 15 s. The ventilometer and gas analysers were

Table 1. Incremental exercise test results comparing $[Hb]_{10}$ with $[Hb]_{14}$

		Younger group (23–45 years) ($n=9$)	Older group (55–66 years) ($n=5$)	All patients ($n=14$)
Peak oxygen consumption (V_{O_2} peak, l/min)	$[Hb]_{10}$	1.70 ± 0.15*	1.45 ± 0.14*	1.61 ± 0.11**
	$[Hb]_{14}$	1.97 ± 0.49	1.77 ± 0.29	1.90 ± 0.11
Peak ventilation (V_E, l/min)	$[Hb]_{10}$	74.3 ± 6.1	75.7 ± 9.3	74.8 ± 4.9
	$[Hb]_{14}$	82.3 ± 7.0	77.2 ± 10.6	80.5 ± 5.7
Peak heart rate	$[Hb]_{10}$	169 ± 4.7	137 ± 4.8	155 ± 6.4
	$[Hb]_{14}$	171 ± 7.4	144 ± 5.2	162 ± 6.8
Work done (kJ)	$[Hb]_{10}$	34.2 ± 4.3**	31.4 ± 6.9	33.2 ± 3.6**
	$[Hb]_{14}$	44.1 ± 5.3	36.5 ± 5.6	41.4 ± 4.0
Peak work rate (W)	$[Hb]_{10}$	147 ± 10**	109 ± 11	134 ± 9**
	$[Hb]_{14}$	160 ± 11	117 ± 9	145 ± 9

Data is expressed for older and for younger groups as well as overall. Values are mean ± SEM. $[Hb]_{10}$ vs $[Hb]_{14}$: *$P<0.05$, **$P<0.01$.

calibrated before and after each test with a standard 3-l syringe and precision reference gases, respectively.

The peak exercise V_{O2} for each patient was compared with predicted values for age-matched, sedentary, healthy controls [21,22]. Since no patient demonstrated a plateau in V_{O2} with increased workrates, the highest V_{O2} was referred to as V_{O2} peak rather than V_{O2} max.

Blood sampling and processing

A 16-G needle was inserted into the arterial side of the arterio-venous fistula, allowing sampling of arterial blood. Resting blood samples were obtained after the subject had been seated for 12 min on the cycle ergometer. Subsequent blood samples were drawn during the last 15 s of each minute of incremental exercise, at fatigue, and at 1, 2, 5, 10, 20 and 30 min post-exercise, with subjects maintaining their seated posture. Samples were analysed for plasma acid–base status and gas tensions (pH, HCO_3, pCO_2, pO_2, electrolyte concentrations (Na^+, K^+, Lac^- and Cl^-), as well as haematocrit (Hct), [Hb]. The total quantity of blood collected in each completed exercise test was ~75 ml.

Measurement of blood volume and Hb mass

Absolute blood volume, and estimates of plasma volume and Hb mass were measured in resting patients using the carbon monoxide dilution technique [23]. In each case, measurements were taken 2 days prior to the exercise test but at the same time relative to dialysis. Briefly, after breathing 100% O_2 for 4 min (via a Hans-Rudolph valve with nose clip), the subject was switched to a low-volume (2 l) closed circuit rebreathing apparatus which had been flushed with O_2 and to which O_2 was added at a rate matching body uptake. After 2 min, the first (control) blood sample of 3 ml was obtained from the arterio-venous fistula and the capped syringe placed on ice. A bolus of CO was then added to the rebreathing system in a volume predicted to change the carbonmonoxyhaemoglobin (HbCO) concentration by approximately 6%, and after 10 min a single blood sample was obtained. Haemoglobin concentration and %HbCO were measured spectrophotometrically using a diode-array spectrophotometer (OSM3, Radiometer, Copenhagen, Denmark). Hb mass and blood volume were then calculated using standard formulae [23].

Plasma K^+ content

The measured plasma volume was used to calculate the arterial K^+ content (Haukka *et al.*, unpublished observations). Calculations were as described previously for the decline in plasma volume with exercise based on changes in [Hb] and Hct and for the ratio of rise in plasma $[K^+]$ per unit work ($\Delta[K^+]$: work, μmol/l/kJ) ratio [24]. The peak exercise plasma K^+ content was calculated from the product of plasma $[K^+]$ and plasma volume after correction for the estimated decline with exercise.

Statistical analyses

Results are reported as mean ± SEM unless otherwise stated. For all analyses an α level of 0.05 was used to determine statistical significance. Comparative data were analysed using Student's paired *t*-test. Correlations were assessed using linear regression analysis, multiple samples were analysed using analysis of variance with repeated measures and post-hoc testing used the Newman–Keuls procedure.

Results

Haemoglobin

Initial (pre-Epoetin) [Hb] ranged from 6.6 to 9.9 g/dl (8.5 ± 0.2 g/dl). Target [Hb] was achieved and maintained (Figure 1) with a significant rise in [Hb] ($P<0.001$). The time taken to complete the study did not differ significantly between those assigned first to reach the higher or lower target [Hb] (13.2 ± 1.1 months, $n=6$ *vs* 17.5 ± 1.7 months, $n=8$).

Blood and plasma volume changes

Red cell volume and Hb mass rose concurrently with [Hb] ($P<0.005$, data not shown). Total blood volume remained unaltered, thus plasma volume fell significantly compared with baseline values (4111 ± 220 ml), both at $[Hb]_{10}$ (3453 ± 184 ml, $P<0.05$) and $[Hb]_{14}$ (2831 ± 117 ml, $P<0.001$). Differences between $[Hb]_{10}$ and $[Hb]_{14}$ were also highly significant ($P<0.001$).

Exercise test

Cardiorespiratory response. The reason given for exercise termination in every test was leg fatigue. Neither resting nor peak heart rate (HR) was altered as the Hb was manipulated. Younger patients achieved a higher peak HR at each targeted [Hb] compared with older patients (Table 1), with mean peak levels close to predicted maximums. The recovery patterns following exercise at both $[Hb]_{10}$ and $[Hb]_{14}$ were virtually identical (data not shown).

The V_{O_2} peak was greater at $[Hb]_{14}$ than $[Hb]_{10}$ ($P<0.01$, Table 1, Figure 2). This was apparent for both older and younger patients. At $[Hb]_{14}$, V_{O_2} peak was $\sim$83% of that predicted for sedentary age-, sex- and weight-matched controls [20,21], and at $[Hb]_{10}$ V_{O_2} peak was 70% of that predicted (Figure 2). Performance relative to that predicted was virtually identical for both younger and older groups. One patient (female, 24 years) reached predicted V_{O_2} peak at $[Hb]_{10}$ and four patients (three in the younger group) at $[Hb]_{14}$. (At baseline all patients were well below predicted levels). There was no difference in peak exercise V_E at different [Hb] (Table 1).

There was a significant improvement in peak work rate (PWR) at $[Hb]_{14}$ *vs* $[Hb]_{10}$ ($P<0.01$, Table 1). This was also evident in the younger group ($P<0.01$) and a similar trend was seen in the older patients ($P=0.08$). Total work performed was 25% higher at $[Hb]_{14}$ than at $[Hb]_{10}$ overall (Table 1).

Plasma ionic changes. Compared with baseline (4.64 ± 0.24 mmol/l), there was an increase in resting plasma $[K^+]$ at both $[Hb]_{10}$ ($P<0.01$) and at $[Hb]_{14}$ ($P<0.001$) (Table 2). The same trend (baseline *vs* $[Hb]_{14}$: 6.37 ± 0.23 *vs* 7.14 ± 0.23 mmol/l, $P<0.01$) was evident at peak exercise (Table 2) and during recovery for up to 10 min (data not shown). Although $[K^+]$ appeared higher at $[Hb]_{14}$ *vs* $[Hb]_{10}$, changes were not significant at any time. Following exercise, plasma $[K^+]$ declined rapidly reaching pre-exercise levels within 2 min in all tests, regardless of [Hb].

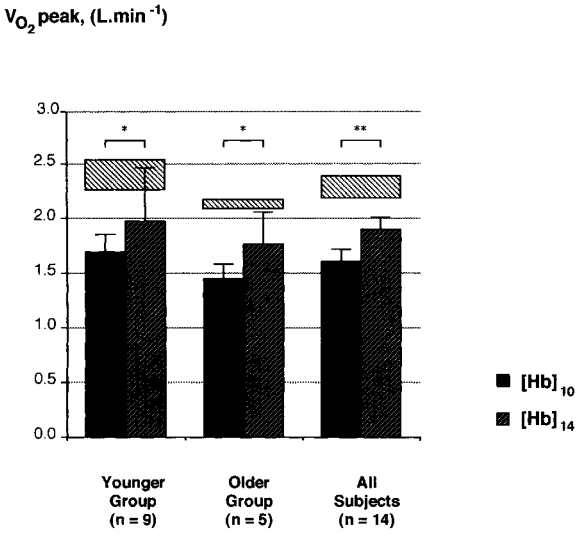

Fig. 2. V_{O_2} peak results at different target [Hb] in younger (age 23–45 years) and older (age 55–66 years) groups as well as for all subjects. Results are compared with those predicted for sex-, age- and weight-matched sedentary controls (horizontal shaded areas represent mean $\pm$ SEM for comparable control group). $^*P<0.05$; $^{**}P<0.01$.

Table 2. Differences at target [Hb] in plasma volume, in $[K^+]$ and K^+ content at rest and peak exercise, and in the $\Delta[K^+]$ work ratio

	$[Hb]_{10}$ ($n=14$)	$[Hb]_{14}$ ($n=14$)
Δ plasma volume, % (rest to peak exercise)	-10.6 ± 0.6	-11.4 ± 0.8
$[K^+]$ (rest), mmol/l	5.05 ± 0.27	5.31 ± 0.20
$[K^+]$ (peak exercise), mmol/l	6.91 ± 0.29	7.14 ± 0.23
Δ K^+ content, mmol (rest to peak exercise)	3.52 ± 0.74	2.84 ± 0.40
$\Delta[K^+]$: work ratio, μmol/l/kJ	61 ± 8	49 ± 7*

$^*P<0.05$.

The rise in $[K^+]$ from rest to peak exercise ($\Delta[K^+]$) remained constant throughout the study (baseline: 1.87 ± 0.18, $[Hb]_{10}$: 1.86 ± 0.20 and $[Hb]_{14}$: 1.84 ± 0.16 mmol/l). With a 9% and 18% improvement in peak work rate at respective target [Hb] however, the $\Delta[K^+]$: work ratio was 24% lower at $[Hb]_{10}$ than in the baseline study (61 ± 8 *vs* 80 ± 12 μmol/l/kJ, $P<0.01$) and 18% lower at $[Hb]_{14}$ (49 ± 7 μmol/l/kJ) than at $[Hb]_{10}$, $P<0.05$, Table 2. There was a significant negative correlation between $\Delta[K^+]$: work ratio and [Hb], $P<0.05$.

The rise in total plasma K^+ content from rest to peak exercise (ΔK^+ content : work ratio) did not differ significantly between the two target [Hb] ($[Hb]_{10}$: 115.9 ± 24.1 μmol/J, $[Hb]_{14}$: 75.8 ± 16.3 μmol/J, $P=$ n.s.), indicating that the observed changes were not due to alterations either in potassium distribution or plasma volume (Table 2).

Arterial plasma lactate concentration ($[Lac^-]$) rose during exercise ($P<0.001$), reached peak values 2 min post-exercise and was still markedly elevated 10 min post-exercise. Peak plasma $[Lac^-]$ was 20% and 24% higher at $[Hb]_{10}$ and $[Hb]_{14}$ respectively (9.80 ± 1.05 and 10.05 ± 1.30 mmol/l), compared with baseline levels (8.13 ± 1.08 mmol/l, $P=$n.s.). The plasma $[H^+]$ was significantly higher at $[Hb]_{14}$ than at $[Hb]_{10}$ both at rest (41.0 ± 1.2 *vs* 37.9 ± 1.2 nmol/l, $P<0.05$) and at peak exercise (48.6 ± 1.8 *vs* 43.5 ± 2.1 mmol/l, $P<0.05$).

Discussion

This study demonstrates a substantial performance advantage in a physiological Hb level compared with subnormal anaemia correction in this selected group of ESRF patients. At $[Hb]_{14}$ patients demonstrated a 25% increase in work performed and an 18% increase in V_{O_2} peak compared with $[Hb]_{10}$. Changes were more marked in younger patients, however trends were ident-

ical in each group. It is possible that the limited numbers might have produced a Type II statistical error in assessing performance in the older patients.

Optimal [Hb] in patients with ESRF are of much interest but remain undefined. Apart from economic and ethical considerations, concern has been raised recently that patients with impaired cardiac function may display a higher mortality in the long-term when maintained at physiological haemoglobin concentrations [25]. This was not observed in this study: no patient was admitted to hospital with myocardial ischaemia during its course or experienced angina during exercise testing. The single death was secondary to biliary sepsis. Limited numbers, exclusion of patients with known myocardial ischaemia and the relatively limited study duration (16 months) could all have contributed to this favourable outcome however, so further conclusions are difficult to draw.

Although there were distinct advantages in achieving a physiological Hb, performance generally remained below predicted levels for age-matched sedentary controls. It is recognized there is a poor correlation between ΔHb and ΔV_{O_2} max in ESRF compared with normal controls [26,27] at least for partial correction of anaemia. The current study suggests that the same holds true at physiological Hb levels (which therefore appear necessary but insufficient for restoration of normal exercise capacity), and that other factors have a critical role in restricting peak performance.

Patients with ESRF have reduced muscular strength and increased fatiguability [28], both of which are known to correlate better with exercise capacity than does [Hb] [8,27]. Studies have documented a variety of skeletal muscle pathologies in ESRF including fibre atrophy [29] and disordered architecture [30], transformation of fibre type [31], impaired oxidative metabolism [12,32–34] and carnitine deficiency [9]. Each could independently contribute to muscular weakness and fatigue although our current understanding is incomplete: numerous discrepancies exist between studies and some of the abnormalities identified at low [Hb] can be partially or fully reversed following epoetin [30].

It is likely, therefore, that other factors are involved. The profoundly sedentary lifestyle of patients with ESRF, inadequate dialysis, malnutrition and concurrent disease can all limit exercise performance. Although patient selection and symptomatic well-being argue against most of these possibilities in the current study, relative and sustained inactivity is common to most patients with ESRF for a variety of reasons. It is possible that the relative capillary rarefaction in the skeletal muscle of dialysis patients demonstrated by Moore and co-workers [12] is a structural sequelum of such inactivity. This has been claimed to limit the exchange of metabolites (thus impairing muscle function) at higher work rates. Although exercise performance is known to increase after training in ESRF [35], whether this is associated with an improved capillary density and whether, in fact, relative rarefaction is the structural correlate of prolonged inactivity remains speculative.

Additional local factors could also be responsible for limitations in exercise performance. Muscle K^+ loss during contraction has been linked with impaired membrane excitability and thus, muscle fatigue [36,37]. Patients with ESRF exhibit marked elevations in arterial [K^+] during exercise [13,38], suggesting large increases in muscle interstitial [K^+] and implicating disturbed K^+ regulation in the early fatigue identified in this condition. We have found grossly impaired [K^+] regulation during incremental exercise in ESRF, with a threefold higher $\Delta[K^+]$: work ratio in anaemic patients with ESRF compared with healthy controls (Sangkabutra *et al.*, unpublished results). Although Clark *et al.* [13] proposed that K^+ regulation during exercise was normal in ESRF, their findings are controversial. First, measurement of [K^+] from the antecubital vein during cycling can be affected by forearm exercise. Secondly, in contrast to their results, most studies support a difference in peak exercise work rate between normal subjects and ESRF patients [2,3,8,10].

There is evidence of impaired Na^+K^+-ATPase activity in uraemic rat muscle which might contribute to disturbed extrarenal K^+ handling during exercise [39–41]. *In vitro* studies have also demonstrated a link between epoetin and Na^+K^+-ATPase activity in rat myocardium [20], suggesting that subnormal [Hb] in ESRF could contribute to impaired extrarenal K^+ regulation in exercise. Therefore, normalization of [Hb] in ESRF might be expected to enhance Na^+K^+-ATPase activity, K^+ regulation and potentially, exercise performance. The present study has shown a progressive improvement in K^+ regulation during exercise, as shown by a progressive reduction in $\Delta[K^+]$: work ratio as [Hb] increased. Peak exercise work rate and V_{O_2} were also successively improved, possibly indicating a link between [Hb], K^+ regulation and exercise performance in ESRF.

In conclusion, although the optimal Hb level for patients with ESRF has yet to be defined, the current study argues favourably for a physiological [Hb] irrespective of age in otherwise healthy patients. Given the paucity of adverse events throughout the study, it is difficult to propose otherwise other than on economic grounds. Even with a normal Hb level however, the exercise potential of such patients remains below normal. Whether this relates to acquired abnormalities in muscle function, to more general systemic effects from sustained uraemia or simply to prolonged anaemia now requires further investigation.

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